

When citing an abstract from the 2025 annual meeting, please use the format below.

[Authors]. [Abstract Title]. Program No. XXX.XX. 2025 Neuroscience Meeting Planner.
San Diego, CA: Society for Neuroscience, 2025. Online.

2025 Copyright by the Society for Neuroscience all rights reserved. Permission to republish any abstract or part of any abstract in any form must be obtained in writing by SfN office prior to publication.

Information is current as of October 27, 2025. See the Neuroscience 2025 Neuroscience Meeting Planner on SfN.org for the most up-to-date information.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: Arizona Biomedical Research Centre Grant #RFGA2022-010-16
NIH Grant #R00MH125329

Title: Metabolic regulation of human cortical cell fate and maturation

Authors: *T. PENNINGTON¹, M. ANDREWS²;

¹Sch. of Biol. Hlth. and Systems Engin., ²Sch. of Biol. & Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

Abstract: The human brain is the most metabolically demanding organ that consumes around 20% of total energy to support neurological activities. During neurodevelopment, the metabolic landscape is dynamically regulated to support transitions in cell state and functional demands. As glycolytic, self-renewing progenitors differentiate, their bioenergetic state is reprogrammed to support the functional requirements of their mature identities. While extensive research has sought to characterize temporal changes in cell types and functional states throughout development, little is known about the metabolic shifts that accompany these developmental transitions in the human cortex. By determining the metabolic programs that govern cell fate decisions, we can better understand the mechanisms that regulate developmental trajectories and identify pathways associated with different phenotypes. This work leverages 3D cortical organoids (hCOs) derived from human pluripotent stem cells to evaluate metabolic states across development and identify bioenergetic programs associated with distinct cell types. To address nutrient requirements in the cortical niche and developmental impact on cellular development, we exposed organoids to standard culture conditions or physiologic levels of key nutrients, glucose and oxygen. Using a combination of molecular and functional assays, we show that glucose and oxygen utilization differentially impact metabolic programs associated with different developmental states. We found that hCOs cultured in physiologic quantities of glucose resulted in increased proportions of cortical stem cells and their neuronal progeny. In contrast, physiologic oxygen conditions suppressed neuronal differentiation. To determine metabolic functions tied to these cellular changes, we performed untargeted metabolomics analyses and functional enrichment of metabolites associated with each condition. The results suggest that oxygen predominantly affects amino acid metabolism, while differential glucose utilization impacts pathways that branch from glycolysis and mitochondria energy oxidation. We then used functional perturbations of metabolic enzymes to determine how differential glucose utilization is tied to these temporal changes. Collectively, this work highlights how metabolism impacts cortical cell state throughout development and provides a framework to determine the mechanisms that regulate developmental trajectories in the human brain.

Disclosures: T. Pennington: None. M. Andrews: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Title: Adducins regulate morphology and fate of neural progenitors during neocortical neurogenesis

Authors: *N. COKORAC¹, N. KALEBIC¹, E. CAPRA²;
¹Human Technopole, Milan, Italy; ²Human Technopole, Milan.

Abstract: The evolutionary expansion of the human neocortex is mediated by an increase in the proliferative capacity of neural progenitor cells. However, the molecular mechanism underlying the increased proliferative capacity of apical and basal progenitors remain poorly understood. Here, we show that three actin-associated morpho-regulatory adducins (ADD1-3) promote abundance of basal progenitors in embryonic mouse and ferret neocortex, and human cortical organoids. Over-expression of adducins in embryonic mouse neocortex increases the number of cell protrusions in basal progenitors, resulting in enhanced proliferative capacity. Conversely, knock-out (KO) of ADD1, an obligatory member of heterodimeric adducin complex, in human cortical organoids reduces the number of protrusions in basal progenitors, and diminishes their proliferative capacity. To gain insight into the mechanism underlying the reduced proliferative capacity of neural progenitors upon ADD1 KO, we performed single-cell RNA sequencing on 11 weeks old wild-type and ADD1 KO organoids. The analysis revealed that ADD1 KO causes accumulation of aberrant neurons, enriched in markers of ER stress, which was validated by immunofluorescence. As the presence of aberrant neurons implies alterations in cell fate dynamics, we inferred cell fate trajectories from our single-cell dataset, and found that ADD1 KO shifts the cell fate of both apical and basal progenitors towards the production of aberrant neurons. To validate computational predictions, we measured mitotic division angles at the ventricular surface of human cortical organoids, and found that ADD1 KO markedly decreases the number of vertical divisions, causing the premature differentiation. Overall, these results show that adducins underlie proliferation and fate of neural progenitors, which are key cellular features underlying progression of mammalian neurogenesis.

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

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: American Heart Association 25PRE1354535

Title: Imp1 orchestrates the timing of radial glial cell development in the mouse neocortex

Authors: *R. AZUR¹, D. FELICIANO², I. ESPINOSA MEDINA³, T. LEE⁴;

¹Dept. of Molecular, Cellular, and Developmental Biology, Univ. of Michigan, Ann Arbor, MI;

²HHMI Janelia Res. Campus, Ashburn, VA; ³HHMI Janelia Res. Campus, Ashburn, VA, ;

⁴Univ. of Michigan / HHMI, Ann Arbor, MI.

Abstract: The proper assembly of neural circuits in the mammalian brain is contingent on the timely generation of neurons during development. We previously identified a mechanism in the *Drosophila* brain where a decreasing temporal gradient of the RNA-binding protein Imp encodes neural stem cell age to specify multiple neuronal fates. In this work, we extend our investigation to Imp1, a mammalian homologue of Imp, and explore its role in murine neocortical development. Using TEMPO to track birth-order dynamics, we demonstrate that sustained Imp1 overexpression during early neurogenesis (E12.5-E13.5) arrests temporal fate progression, shifting neuronal populations toward deeper cortical layers V-VI. Immunostaining with cortical layer markers Cux1 and Ctip2 confirmed that this laminar repositioning results from genuine changes in neuronal identity rather than mere migratory defects. Temporal window-specific manipulations identified a critical developmental window during which Imp1 activity induces marked accumulation of neurons in the subplate region. Live imaging of organotypic cultures revealed that Imp1-overexpressing cells at this window exhibit impaired radial migration toward the cortical plate, accounting for the observed subplate accumulation phenotype. Strikingly, mid-temporal Imp1 overexpression also led to the genesis of ectopic glial-like foci distributed throughout the cortical plate that emerges postnatally, indicating a broader role of Imp1 in cell fate specification beyond neuronal identity alone. Collectively, our findings establish Imp1 to be a critical temporal pacemaker, orchestrating developmental transitions in radial glial progenitors and controlling both neuronal fate decisions and migration. This work advances our understanding of the molecular timing mechanisms crucial for the structured emergence of neuronal diversity in the mammalian cortex.

Disclosures: R. Azur: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS110586
NIH Grant NS120664

Title: Stem cell dynamics during neurogenesis and ependymogenesis in the developing ventricular-subventricular zone

Authors: *S. P. BERNIER, M. MAJID, J. C. CONOVER;
Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT

Abstract: Understanding how neural stem cells (NSCs) generate ependymal cells and sustain neurogenesis in the ventricular-subventricular zone (V-SVZ) is essential for understanding normal brain development and the pathogenesis of disorders such as hydrocephalus. Initial studies focused on the medial wall (MW) of the lateral ventricle, which, as in humans, is a key site of neurogenesis and ependymogenesis that then undergoes postnatal NSC depletion and is a key site of neurogenesis and ependymogenesis. Early embryonic NSC divisions are largely symmetric, expanding the stem cell pool. To investigate neonatal to postnatal NSC lineage dynamics, we performed genetic fate mapping using Nestin-CreERT2:Rosa26-tdTomato mice, inducing recombination with tamoxifen at postnatal day 5 (P5) and P12. EdU was administered 24 hours later to label proliferating cells, and brains were collected at P7 and P14. Whole mounts and coronal sections were immunostained for β -catenin, S100 β (ependymal cells), GFAP (astrocytes), DCX (neuroblasts), and EdU. To assess the timing of neurogenic decline, CD1 mice were injected with EdU 36 hours before collection at P3, P7, P14, and P30, followed by immunostaining for DCX, EdU, and cleaved caspase-3 to evaluate neuroblast generation and apoptosis. Preliminary data indicates a developmental shift in NSC division patterns. Analysis of ependymogenesis from P5-P7 revealed that asymmetric divisions predominate, producing one NSC and a S100 β ⁺ ependymal cell. By P12-P14, terminal symmetric divisions generating two S100 β ⁺ ependymal cells became more frequent, coinciding with a rapid decline in neurogenesis, indicating a transition in NSC fate determination. By P30, little, if any, neurogenesis is observed along the MW based on near-complete loss of EdU⁺, DCX⁺ neuroblasts. Notably, we saw negligible caspase-3⁺ cell death, implying that reduced neurogenesis is due to NSC depletion through terminal symmetric divisions rather than apoptosis. In summary, these findings highlight P7-P12 as key inflection points in MW NSC dynamics, marking the change in dominance from asymmetric division to terminal symmetric division. By P14, NSC output has decreased significantly, and the ependymal barrier has matured. By characterizing NSC lineage trajectories and division modes across development, our studies provide a framework for understanding both normal brain maturation and its dysregulation in neurodevelopmental diseases such as congenital hydrocephalus.

Disclosures: S.P. Bernier: None. M. Majid: None. J.C. Conover: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Title: Role of RDP in the maintenance of neural stem cell properties

Authors: *Y. YOON, K. YOON;
Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Normal brain development relies on the tightly regulated balance of neural stem cell (NSC) self-renewal and differentiation to ensure orderly cortical lamination. Disruptions in this balance are implicated in neurodevelopmental disorders such as microcephaly, yet the underlying molecular mechanisms remain poorly understood. Here, we identify RDP, a nuclear HMG box-containing protein, as a critical regulator of NSC maintenance. In this study, we show that RDP is required for the maintenance of NSC properties *in vitro*. Strikingly, the depletion of RDP *in vivo* leads to morphological and migration defects in newborn neurons, implicating defective neurogenesis. Transcriptome analysis reveals upregulation of the senescence-associated gene p21. Mechanistically, we identify RDP as a novel binding partner of p53 that suppresses p53-mediated transcriptional activation of p21. Together, these findings uncover a previously unrecognized role for RDP in inhibiting p21 to support proper cortical development.

Disclosures: Y. Yoon: None. K. Yoon: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NCI CA235749
NIH/NIGMS GM143276
NIH/NCI CA274595
NSF CAREER award IOS-2143711
NSF MRI Award DMR-1625733

Title: In vivo cilium proteomics reveals new regulators of cortical development

Authors: *O. J. TORRES GUTIERREZ¹, X. LIU², G. KAUR¹, X. GE³;
¹Quantitative and Systems Biol., ²Mol. and Cell Biol., Univ. of California, Merced, Merced, CA;
³Mol. and Cell Biol., Univ. of California Merced, Merced, CA

Abstract: In the developing brain, the primary cilia of radial glial cells extend from the surface of the lateral ventricle, serving as the signaling hub to integrate environmental cues critical for brain formation. Dysfunctions in ciliary proteins contribute to a wide range of brain structural abnormalities in ciliopathies, yet identifying the bona fide ciliary protein components in the brain remains a significant challenge. Here, using proximity labeling and quantitative proteomics, we

systematically charted proteins localized to the cilia of radial glial cells in the dorsal and ventral regions of the embryonic brain. From this dataset, we identified cohorts of new molecules intrinsic to the cilia at distinct regions of the developing brain. We validated the cilium localization of several components of the translation machinery and studied the mechanistic roles of ciliary candidates previously linked to brain malformation, including Marcks, a key regulator of radial glial polarity, and Ckap2l, a protein associated with Filippi syndrome. These results revealed previously unrecognized ciliary mechanisms that regulate brain development. Thus, our brain proteomic dataset provides a unique resource for understanding ciliary functions in brain development and the molecular etiology of developmental disorders.

Disclosures: O.J. Torres Gutierrez: None. X. Liu: None. G. Kaur: None. X. Ge: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: Society of Hellman Fellows
Glaucoma Research Foundation
Melza M. and Frank Theodore Barr Foundation
NINDS (U01NS136405)
NSF CRCNS 2309039
BrightFocus Foundation (NGR)

Title: A Multiomic Atlas of the Mouse Retina

Authors: *M. A. PO¹, T.-K. CHU², N. M. TRAN³, K. SHEKHAR¹;

¹Chem. and Biomolecular Engin., Univ. of California, Berkeley, Berkeley, CA; ²Dept. of Mol. and Human Genet., Baylor Col. of Med., St. Louis, MO; ³Mol. and Human Genet., Baylor Col. of Med., HOUSTON, TX

Abstract: The mouse neural retina is made up of about 130 distinct cell types that interface to perform computations on incoming light stimuli. These neuronal types can be categorized into five main classes: photoreceptor, horizontal, bipolar (BCs), amacrine (ACs), and retinal ganglion cells (RGCs). In recent years, single-cell RNA sequencing (scRNA-seq) has been used to profile these cell types, giving rise to a comprehensive understanding of the transcriptional diversity of the retina. However, the regulatory landscape that engenders this diversity is not well understood. The dynamics of transcriptional regulation in these cells are ultimately governed by epigenetics. The development of single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq) has provided the ability to profile accessible chromatin regions across the genome at the level of single cells, which in turn empowers the identification of cell-type specific epigenetic signatures. Combining this technology with scRNA-seq then allows for a

mapping of candidate regulatory regions to their target genes, enabling an understanding of the gene regulatory landscapes that give rise to cell-type specific transcriptional programs. Here, we generated a multiomic atlas of the mouse retina consisting of paired scRNA-seq and snATAC-seq from the same set of cells. Our collection includes cells from each of the five neuronal classes of the retina, as well as sufficient cells to explore type-level differences within the BCs, ACs, and RGCs. At both the class- and type-levels, we used the paired accessibility and expression data to identify correlation-based links between regions and genes, then used sequence information to identify transcription factor (TF) binding motifs within candidate regulatory regions. This information was then used to build cell-type specific gene regulatory networks (GRNs) that link TFs to their target genes via their regulatory regions of action. For example, in RGCs, we identified GRNs linking 54 TFs, 1758 regulatory regions, and 1104 target genes, many of which are active in a small subset of cell types. We then utilize our GRNs to explore the regulation of functionally relevant genes, including melanopsin (Opn4), within a subclass of RGCs known as the intrinsically photosensitive RGCs, which are implicated in non-image-forming visual functions such as circadian rhythm entrainment and the pupillary light reflex. Finally, we explore the use of neural network-based models to predict gene expression from chromatin accessibility and TF expression data and demonstrate their use in performing in silico perturbation experiments.

Disclosures: M.A. Po: None. T. Chu: None. N.M. Tran: None. K. Shekhar: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSTC 113-2320-B-A49 -017 -MY3

Title: Supt4h specifically directs the developmental commitment of neural progenitors into the pre-Bötzinger complex

Authors: *F.-Y. LIN^{1,2}, P. LI¹, W. LEE¹, C.-K. SU³, Y.-M. CHANG³, C.-Y. LIN¹, Y.-T. YAN³, S.-J. CHOU^{2,4}, T.-H. CHENG^{1,2,5};

¹Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; ²Taiwan Intl. Grad. Program in Interdisciplinary Neuroscience, Natl. Yang Ming Chiao Tung Univ. and Academia Sinica, Taipei, Taiwan; ³Inst. of Biomed. Science, Academia Sinica, Taipei, Taiwan; ⁴Inst. of Cell. and Organismic Biology, Academia Sinica, Taipei, Taiwan; ⁵Brain Res. Center, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Spatial-temporal transcription of particular sets of genes governs the commitment of progenitor cells into neurons with diverse physiological functions in the course of neuronal development. It has been shown that pre-Bötzinger complex (preBötC), a nucleus in the medulla

responsible for the inspiratory breathing rhythm, is derived from *Dbx1*-lineage progenitors; however, the details of the commitment process, at both the cellular and gene expression levels, for the genesis of preBötC remain elusive. Here, using neural-specific conditional knockout (cKO) mice, we found that the absence of Supt4h, a transcription elongation factor required for effective transcription of genes in a DNA context-dependent manner, led to a selective failure of preBötC development, identifying it as a critical regulator of inspiratory neuron specification. Neural-specific knockout of Supt4h resulted in neonatal lethality with disrupted preBötC formation, while the other respiratory rhythm generator parafacial respiratory group (pFRG), remained intact. *Dbx1*-lineage progenitors are committed to preBötC neurons between E9.5 and E10.5. Deletion of Supt4h specifically in *Dbx1*-lineage cells led to increased apoptosis within rhombomere 6 during this critical developmental window. Single-cell RNA sequencing revealed a disrupted transcriptomic trajectory from progenitor cells to preBötC precursors. Our study identifies Supt4h as a key regulator in the differentiation of *Dbx1*-lineage progenitors into preBötC neurons and reveals a unique set of genes that are essential and transcriptionally regulated by Supt4h during this commitment process.

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

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R37 NS095733 to KJM
NIH R01 NS122902 to KJM and MEH

Title: Defining transcription factors driving human cerebellar cell fates

Authors: K. BLAKEMAN¹, M. SALEH¹, A. ERICKSON³, P. HALDIPUR⁴, G. HE⁵, Z. SCHAPIRE⁶, N. CHENG⁷, J. ZHAO⁷, M. E. HATTEN⁷, *K. J. MILLEN^{4,2};
²Pediatrics, ¹Univ. of Washington, Seattle, WA; ³Univ. of Toronto, Toronto, ON, Canada;
⁴Seattle Children's Res. Inst., Seattle, WA; ⁵Seattle C, Seattle, WA; ⁶The Rockefeller Univ., New York, NY; ⁷Develop. Neurobiol, Rockefeller Univ., New York, NY

Abstract: The cerebellum is a critical brain region with central roles in sensory-motor control and non-motor functions: cognition, emotion, and language. Distinct neuronal subtypes play specialized roles in cerebellar function. GABAergic neuronal lineages originate from the ventricular zone, while glutamatergic lineages originate from the rhombic lip. The molecular mechanisms that drive specification of each lineage in the developing cerebellum remain largely unknown. Studies in mice and chick have identified a few transcription factors that drive cerebellar cell fates. However, these studies are limited by the fact that cerebellar development in

these species is very rapid with just a short window of time within which to modulate gene function. Further, high throughput, combinatorial functional studies are difficult to implement. Finally, while much of cerebellar development is conserved across species, recent studies have identified human species-specific features. We are therefore leveraging extensive normal human developing cerebellar single cell RNAseq and ATACseq datasets to identify candidate transcription factors likely to drive human cerebellar cell fates based on *in silico* perturbation of predicted gene regulatory networks. We will then validate these predictions in a novel 2D cerebellar differentiation culture system using Perturb-seq technology. We have demonstrated that this culture system reliably replicates the early lineage specification of native human cerebellar development. Our experiments will be the first to systematically assess the function of multiple transcription factors in the specification and differentiation of cerebellar lineages. In the longer term, an *in vitro* system for directed differentiation of cerebellar lineages will be an invaluable model for human cerebellar disorders including Dandy-Walker malformation, spinal cerebellar ataxias and medulloblastoma, providing a platform for assessing disease mechanisms and potential new therapeutic agents.

Disclosures: K. Blakeman: None. M. Saleh: None. A. Erickson: None. P. Haldipur: None. G. He: None. Z. Schapire: None. N. Cheng: None. J. Zhao: None. M.E. Hatten: None. K.J. Millen: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIHR

Title: Msx1 as a master regulator of the cerebellar glutamatergic lineage.

Authors: M. KE¹, J. T. YEUNG¹, M. RAHIMI-BALAEI², E. CHEN³, A. UDUMULLAGE⁴, *D. GOLDOWITZ¹;

¹Med. Genet., ²Human Anat. and Cell Sci., ³Biochem., ⁴Neurosci., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The cerebellum is a major part of neural circuits responsible for coordinating movements and cognitive processing. Cerebellar abnormalities are observed in many neurodevelopmental disorders. The rhombic lip, the germinal zone that gives rise to the entire cerebellar glutamatergic lineage, has also recently been established as the origin of the cells capable of forming medulloblastoma. Understanding the molecular mechanisms underlying cerebellar development will yield important insights into the pathophysiology of cerebellar disorders and potentially lead to novel therapeutic interventions. The current dogma of glutamatergic neuron development places the transcription factor *Atoh1* as the key regulator of

glutamatergic fate. However, our recent work suggests that the transcription factor *Msx1* may precede *Atoh1* in the determination of glutamatergic fate, motivating the present study. We hypothesize that *Msx1* activates the gene regulatory network that specifies and maintains the rhombic lip progenitors, prior to the activation of *Atoh1* and their exit from the rhombic lip. To test this hypothesis, we conducted two sets of experiments. In our first set of experiments, we are studying the role of *Msx1* in cerebellar development by characterizing the phenotype of the *Msx1* knockout (KO) mouse. Our initial findings indicate a decreased and altered shape of the KO cerebellum versus the wild type at embryonic day 18, which may reflect reduced glutamatergic neuron production. The loss of some of the cerebellar nuclear neurons as well as the disorganization of the nascent unipolar brush cells, granule cells, and Purkinje cells have also been observed. Immunostaining for neuron type-specific markers as well as examination of earlier embryonic timepoints is underway. In our second set of experiments, the developmental fate of *Msx1*-expressing progenitors and the migratory history is being explored using genetic inducible fate mapping. *Msx1*-CreERT2 mice are crossed with red fluorescent protein (RFP) reporter mice, allowing for spatiotemporal labeling of *Msx1*-expressing cells and their progeny after timed tamoxifen injections. Our initial findings have demonstrated that *Msx1*-expressing progenitors labeled at embryonic day 10 contribute to all three glutamatergic neuron types in the cerebellum at embryonic day 18. Taken together, our initial findings support our hypothesis of *Msx1*'s role in glutamatergic neuron development, warranting further characterization of *Msx1* and its involvement in the rhombic lip progenitors' gene regulatory network.

Disclosures: M. Ke: None. J.T. Yeung: None. M. Rahimi-Balaei: None. E. Chen: None. A. Udumullage: None. D. Goldowitz: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: K00MH139443

Title: Development of raphe nuclei organoids to explore neurodevelopment and cell fate

Authors: *R. D. HERNANDEZ¹, S. A. SLOAN²;

²Human Genet., ¹Emory Univ., Atlanta, GA

Abstract: Serotonin is a critical neuromodulator in central nervous system development, yet its role in glial maturation and regional specification has remained poorly understood, particularly in human models. To address this gap, we developed a human hindbrain-derived raphe organoid model that mimicked the emergence of serotonergic neurons and their surrounding environment. In parallel, we generated cortical organoids to compare region-specific effects of serotonin on glial development. Using these models, we examined the impact of serotonin exposure at early

and late developmental stages. We conducted transcriptomic analyses to identify serotonin-induced changes in astrocyte gene expression, with a focus on markers of maturation, regional identity, and functional specialization. This study provides a foundational framework for understanding serotonin's influence on human glial differentiation and offers insights into how altered serotonergic signaling may contribute to neurodevelopmental disorders.

Disclosures: R.D. Hernandez: None. S.A. Sloan: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Title: Differential Activity of the Transcription Factor Nkx2.1 in Embryonic Mouse Brain, Lung, and Thyroid

Authors: *M. T. C. MANION¹, Y. ZHANG², T. J. PETROS³;

¹NICHD, Bethesda, MD; ²NICHD, NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Bethesda, MD; ³Developmental Neurosci. Br., NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Rockville, MD

Abstract: Individual transcription factors are often expressed in multiple cell and tissue types during development, but with distinct genomic targets. This in part explains why human variants in transcription factors can lead to complex, multi-organ phenotypes that are challenging to treat. Mechanisms that guide differential transcription factor activity in distinct tissues are not well understood. Possible mechanisms that guide transcription factor specificity are (1) tissue-specific chromatin accessibility, (2) tissue-specific co-factors and adaptor proteins, and/or (3) tissue-specific genomic binding motifs that recruit a specific set of transcription factors. The transcription factor Nkx2.1 is expressed in the embryonic thyroid, lung, hypothalamus, and medial ganglionic eminence (MGE), where it plays critical roles in development of these tissues. In the MGE, Nkx2.1 serves as a 'master regulator' for all MGE-derived GABAergic inhibitory neurons, while in the lung, it regulates differentiation of alveolar cell subtypes. Humans with NKX2.1 mutations suffer from the aptly named Brain-lung-thyroid syndrome and display neurodevelopmental symptoms, impaired respiration and hypothyroidism. Thus, Nkx2.1 represents an ideal candidate to explore differential transcription factor binding in distinct tissues and its role in disease. To probe differential Nkx2.1 binding in these tissues, we collected the MGE, hypothalamus, lung, and thyroid at embryonic day 13.5 (E13.5) and performed CUT&RUN to identify Nkx2.1 binding sites in each tissue. We also performed single cell Multiome assays to analyze gene expression and chromatin accessibility in Nkx2.1-expressing cells. By integrating gene expression, chromatin accessibility, and Nkx2.1 binding sites, we have gained mechanistic insight into differential Nkx2.1 function in distinct tissue. At some loci, differential accessibility in tissues drives differential Nkx2.1. binding. At other loci, accessibility

is similar between tissue, implying that other regulatory mechanisms drive this differential binding. These insights improve our understanding of not only Nkx2.1 regulation during development, but also how transcription factors regulate distinct genetic programs in different tissue during development.

Disclosures: M.T.C. Manion: None. Y. Zhang: None. T.J. Petros: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: Japan Society for the Promotion of Science

Title: Schwann cell precursor-derived sympatho-adrenal cells and their contribution to neuroblastoma

Authors: *H. ENOMOTO;
Kobe Univ. Grad. Sch. of Med., Kobe, Japan

Abstract: In jawed vertebrates, the sympathetic ganglia and adrenal medulla are conserved structures located ventral to the vertebral column. However, in a subset of neuroblastoma—a pediatric malignancy with sympathoadrenal (SA) features—tumors arise in ectopic, multifocal sites outside these canonical locations, suggesting an additional, previously unrecognized developmental origin for SA cells. Here, we demonstrate that Schwann cell precursors (SCPs) distributed along peripheral nerves can give rise to ectopic SA cells. A subset of SCPs exhibits a latent predisposition to express a transcription factor essential for SA lineage specification. Suppression of this transcriptional activity is required to maintain glial identity and depends on the dosage of an upstream regulatory gene. Loss of one allele of this regulatory gene disrupts suppression, leading to widespread ectopic SA differentiation. This effect is further amplified by an oncogenic driver mutation associated with neuroblastoma. Single-cell RNA sequencing identified a second transcription factor, previously linked to high-risk neuroblastoma, as being downregulated during the SCP-to-SA cell transition. Disruption of this factor alone was sufficient to elevate transcripts of the SA-specifying gene and promote ectopic SA differentiation. These findings establish SCPs as a systemic source of SA cells and reveal that failure to suppress their neurogenic potential may drive aberrant SA differentiation, potentially contributing to neuroblastoma and related neurocristopathies.

Disclosures: H. Enomoto: None.

Poster

PSTR001: Mechanisms of Cell Fate

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR001.14/A14

Topic: A.07. Development of Neural Systems

Support: NIH IRP funding HD008962

Title: A Perturb-seq CRISPR screen to identify transcription factors promoting CGE-derived interneurons

Authors: *A. CHAUHAN¹, D. R. LEE², T. J. PETROS³;

¹NICHD, NIH, Bethesda, MD; ²California Inst. for Regenerative Med. (CIRM), California, CA;

³Developmental Neurosci. Br., NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Rockville, MD

Abstract: Forebrain GABAergic interneurons originate from the medial and caudal ganglionic eminence (MGE & CGE). While some genes driving MGE-derived interneuron development have been well-characterized, mechanisms regulating CGE-derived interneurons remains largely unexplored. Interestingly, humans have an increased percentage of CGE-derived interneurons relative to mice, and some diseases such as tuberous sclerosis complex (TSC) are directly linked to dysfunction of CGE cells. Thus, defining genes that drive CGE cell fate is critical to understand both normal development and disease etiologies. Here we perform a CRISPR Perturb-seq experiment to identify candidate transcription factors (TFs) that promote CGE fate. We generated 2 mESC lines with Cas9 linked to an activator or repressor. We retrofitted these mESCs with a fluorescent CGE reporter (*Nr2f2-RFP*) to detect CGE-fated cells. Further, we generated a Lentiviral library of gRNAs targeting ~900 TFs expressed in the embryonic mouse brain. By collecting Lentiviral-infected RFP+ cells, we will identify candidate genes whose activation or repression promotes CGE fate.

Disclosures: A. Chauhan: None. D.R. Lee: None. T.J. Petros: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.01/A15

Topic: A.03. Axon and Dendrite Development

Support: T32 GM153602-01
IOS-1853719
R35 NS097340

Title: Stuck in the Middle: The Role of the Dystrophin Glycoprotein Complex in Midline Axon Guidance

Authors: *T. FITCH^{1,2}, S. GAGNON², G. J. BASHAW²;

¹Perelman Sch. of Med., ²Univ. of Pennsylvania, Philadelphia, PA

Abstract: A critical step in the development of neural circuitry is when commissural axons cross the midline of the central nervous system to establish bilateral connectivity. This crossing is guided by a series of cues in which the axon is first attracted to, then repelled from the midline. The midline repellent Slit binds to the receptor Roundabout (Robo) to trigger repulsion via cytoskeletal remodeling. To prevent premature repulsion in *Drosophila*, the sorting receptor Commissureless (Comm) targets Robo for degradation. After crossing, Comm expression rapidly decreases, allowing Robo to accumulate and sensitize the axon to Slit, ultimately inducing repulsion and preventing recrossing. Although Comm's role in degrading Robo is established, this mechanism alone cannot fully explain the spatiotemporal regulation of repulsive signaling. Because actin remodeling is a key downstream output of repulsion, we hypothesized that Comm may also impact the expression or function of cytoskeletal regulators. Using affinity purification-mass spectrometry in embryonic *Drosophila* neurons, we identified both Dystrophin (Dys) and Dystroglycan (Dg), core components of the Dystrophin Glycoprotein Complex (DGC), as Comm interactors. Dys, a cytoskeletal scaffold with a WW domain, links the extracellular matrix to the intracellular actin cytoskeleton through binding Dg. Co-immunoprecipitation confirmed the Comm-DGC interaction and showed that mutation of the conserved PY motifs in Comm reduced Dys binding significantly compared to wild-type Comm (n=3 replicates). Further, endogenous reporter lines revealed Dys expression in both neurons and glia during commissural axon crossing. To assess a function for Dys in midline guidance, we tested genetic interactions between *Dys* and the Slit-Robo pathway. Loss of *Dys* enhances ectopic midline crossing in a *slit, robo/+* sensitized background, with ~47% of segments showing guidance errors versus ~20% in controls (n = 20 embryos/genotype; p = 0.0258). A *Drosophila* line expressing a mutant form of *Dys* lacking the Dg-binding domain shows similar defects, suggesting that the Dys-Dg interaction is required for DGC function in repulsion. These findings support a model in which Comm binds the DGC through PY-WW interactions with Dys to coordinate Robo trafficking with membrane-cytoskeletal anchoring. Given the DGC's known role in neuromuscular disease, this work not only reveals how its coordination of ECM and cytoskeletal interactions supports axon guidance but may also offer insights into mechanisms underlying neurodevelopmental disorders.

Disclosures: T. Fitch: None. S. Gagnon: None. G.J. Bashaw: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.02/A16

Topic: A.03. Axon and Dendrite Development

Support: NIH IRTA

Title: Neuregulin-1 (Nrg1) signaling orchestrates cholinergic axon outgrowth and synapse formation during early development

Authors: *A. CICEU¹, C. ZHONG³, D. FREEMAN², P. RAJEBHOSALE⁴, L. W. ROLE⁵, D. A. TALMAGE⁶;

¹Natl. institute of Neurolog. Disorders and Stroke (NINDS), ²NIH, Washington, DC; ³NINDS, NIH/NINDS, Bethesda, MD; ⁴NINDS, NIH/ NINDS, Bethesda, MD; ⁵NINDS, ⁶NINDS, Bethesda, MD

Abstract: The Neuregulin-1 Type III isoform (CRD-Nrg1) and its receptors ErbB4/ErbB3 comprise a bidirectional signaling pathway critical for axonal growth, synapse formation, and neuronal survival. Axonal CRD-Nrg1 is required for the formation of stable cholinergic synapses at the neuromuscular junction and knockout mice die due to failure of diaphragm innervation. Cholinergic neurons of the basal forebrain contain highly complex axonal arbors and form synapses throughout the brain. However, the specific contributions of CRD-Nrg1 signaling to the development of basal forebrain cholinergic axons remains largely unexplored.

To address this gap, we developed a basal forebrain microexplant preparation from neonatal mice to examine cholinergic axon maturation. Cholinergic axons extend from these explants and exhibit progressively increased levels of vesicular acetylcholine transporter (VACHT), a marker of cholinergic pre-synaptic terminals. Stimulation of CRD-Nrg1 in cholinergic axons enhanced both axon outgrowth and the expression of VACHT.

Our next steps involve dissecting the mechanism(s) by which axonal CRD-Nrg1 signaling influences VACHT levels. Specifically, we will examine whether axonal CRD-Nrg1 signaling modulates VACHT levels via local mechanisms, involving trafficking and/or local synthesis, or via signaling from the axon to the nucleus affecting VACHT gene expression.

This ex-vivo preparation of basal forebrain microexplants provides a tractable platform for studying cholinergic axon growth and development in granular detail. To date, our results support the importance of CRD-Nrg1 in the development and maturation of basal forebrain cholinergic axons.

Disclosures: A. Ciceu: None. C. Zhong: None. D. Freeman: None. P. Rajebhosale: None. L.W. Role: None. D.A. Talmage: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.03/A17

Topic: A.03. Axon and Dendrite Development

Support: MOE2018-T2-2-103
MOH-000212
MOH-000207

Title: Ivns1abp deficiency impairs growth cone structure and function via altered drebrin phosphorylation

Authors: *S.-M. CHOU¹, F. YUAN², S.-C. ZHANG^{2,1};
¹Duke-Nus Grad. Med. Sch., Singapore, Singapore; ²Sanford Burnham Prebys, La Jolla, CA

Abstract: We identified an undiagnosed disease characterized by premature aging and severe neuropathy. Whole-exome sequencing revealed a point mutation, c.758T>G, in the IVNS1ABP gene. By generating induced pluripotent stem cells (iPSCs) and their isogenic pairs from patients and differentiating them into cortical neurons, we observed smaller growth cone sizes in the mutant neurons, along with reduced actin-microtubule contacts and altered microtubule configurations. In IVNS1ABP-deficient neurons, we detected an increased number of Drebrin/actin puncta and a significant decrease in Drebrin phosphorylation. Furthermore, we found reduced ARHGEF11 levels in IVNS1ABP-deficient neurons, accompanied by increased ubiquitination. Since ARHGEF11 bridges Cdk5 and Drebrin, its loss likely disrupts this interaction, impairing Drebrin phosphorylation. We propose that the IVNS1ABP mutation enhances ARHGEF11 ubiquitination and degradation, thereby impairing Drebrin phosphorylation and disrupting actin-microtubule interactions in growth cones, ultimately contributing to defective neural development.

Disclosures: S. Chou: None. F. Yuan: None. S. Zhang: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.04/A18

Topic: A.03. Axon and Dendrite Development

Support: Parkinson's UK
Kavli KARD award
iotaSciences Ltd.
BBSRC
Aligning sciences across Parkinson's
Brasenose College, University of Oxford
St Peter's College, University of Oxford

Title: Engineering human neuronal circuits using microfluidics with fluid walls

Authors: *J. A. E. MORGAN¹, R. MÁRQUEZ GÓMEZ², A. SPYROU¹, F. NEBULONI⁴, Q. DO⁵, A. MEHTA², C. LANG³, R. WADE-MARTINS², E. WALSH¹;

¹Dept. of Engin. Sci., ²Dept. of Physiol. Anat. and Genet., ³Ctr. for Human Genet., Univ. of Oxford, Oxford, United Kingdom; ⁴The Francis Crick Inst., London, United Kingdom; ⁵Genome Inst. of Singapore, Singapore, Singapore

Abstract: Modelling human brain cells within functional circuits is essential in advancing our understanding of many neurological disorders. Current knowledge of brain circuitry is largely derived from animal studies, while work in humans has mostly been limited to imaging in vivo or post-mortem analysis. Recently, a multidisciplinary team has developed new microfluidic tools to build circuits of living human neurons in the lab. We present and validate a system for long-term culture of neuronal circuits in microenvironments confined by fluid walls - made by utilizing the immiscibility of aqueous cell media and the bio-inert fluorocarbon, FC40. Fluid walls are used to create biocompatible, fully accessible microfluidic circuits directly within standard tissue cultureware that can dynamically change in both space and time. Circuits are formed by reshaping a thin layer of culture media using a jet of FC40, directed by a fluid printer. Using this approach, any 2D design can be fabricated, and fluid added to generate pressure gradients, creating a functional microenvironment. The main circuit affected in Parkinson's disease is comprised of cortical, striatal, and dopaminergic neurons. We print fluid-walled 'dumbbell' circuits and demonstrate that such microenvironments support the long-term culture of all three neuronal subtypes derived from human iPSCs (hiPSCs). Selectively adding fluid to chambers generates pressure gradients within the circuit, enabling effective confinement of cell types. This facilitates spatial separation for co-culture of different cell types, compartmentalization of somas and dendrites from axons, and unidirectional axon projection. We also show a triple-chamber system allowing coculture of all three neuron types, modelling the full cortico-striatal-dopamine neuronal circuit. All regions of the circuit are fully accessible and can be reconfigured mid-experiment, users can isolate and harvest from specific regions (cells/media) of interest. Control over the compartmentalization and directionality of neuronal connections based on fluid dynamics offers an efficient and highly reproducible system for development of human neuronal circuits assays. Finally, we show that these microenvironments can be fabricated directly within commercially available multi-electrode array plates (MEA), enabling monitoring of signaling between separated neuron sub-groups.

Disclosures: J.A.E. Morgan: A. Employment/Salary (full or part-time): iotaSciences Ltd. provided financial support to J.A.E.M. R. Márquez Gómez: None. A. Spyrou: None. F. Nebuloni: A. Employment/Salary (full or part-time): iotaSciences Ltd. provided financial support to F.N. Q. Do: None. A. Mehta: None. C. Lang: None. R. Wade-Martins: None. E. Walsh: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); E.J.W. co-founded, and holds equity in, IotaSciences Ltd. Oxford University Innovation has filed patent applications on behalf of E.J.W..

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.05/A19

Topic: A.03. Axon and Dendrite Development

Support: NSF CRCNS 2112862

Title: Morphological and Stochastic Properties of Transgenically-Individualized Serotonergic Fibers in the Mouse Telencephalon

Authors: *J. H. HAIMAN¹, H. ROOSTAEYAN², N. ELYASI², E. LEDAKAITE², C. ARQUETTE², M. NAWAZ², S. JANUSONIS²;

¹UC Santa Barbara, Santa Barbara, CA; ²Psychological & Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Virtually all neural networks in vertebrate brains operate inside dense meshworks of axons that are not captured by connectivity graphs and have no analogs in current artificial neural networks (ANNs). Many of these axons store and release serotonin, an extensively-studied neurotransmitter, but their fundamental function remains enigmatic. Serotonergic axons (fibers) appear to support neuroplasticity, with many implied roles across neuroprocesses, and they themselves are highly plastic, with a strong regenerative potential in adult mammalian brains. Serotonergic fibers are packed at different densities in different brain regions, which is the result of the dynamics of a large number of individual fibers, each of which can make trajectory decisions independently of others. Our experimental and theoretical work seeks to bridge the “behavior” of single serotonergic fibers (a sub-micrometer scale) and the self-organization of many serotonergic fibers in anatomical nuclei and laminae (a sub-millimeter scale). Methodologically, this approach is based on high-resolution microscopy, transgenic systems, and stochastic modeling. This study provides the first detailed description of individually-tagged serotonergic axons in selected telencephalic regions (cortical and subcortical) of the mouse brain. By using our previous implementation of the Brainbow toolbox in the serotonergic system, mouse serotonergic fibers were labeled with random intensity combinations of three fluorophores, imaged in three dimensions with confocal microscopy, and modeled by using time-series analysis and continuous-time anomalous diffusion models. At the qualitative level, all examined regions contained serotonergic fibers of diverse identities and morphologies, many of which traveled in close proximity to one another. In particular, fibers with prominent varicosities (bead-like dilations) were found in the immediate vicinity of smooth fibers, raising questions about the origin and age of fibers occupying the same microscopic tissue volume at the same time. To obtain quantitative data, individual fibers were traced in confocal stacks, computationally sectioned along the trajectory with dense sampling, and the obtained series of cross-sectional areas were treated as a stochastic process. We show that the dynamics of the serotonergic fiber diameter along the fiber path can be modeled as a low-order autoregressive moving-average (ARMA) process or the subdiffusive fractional Brownian motion (FBM), with implications for the growth and functional equilibria of these fibers.

Disclosures: J.H. Haiman: None. H. Roostaeyan: None. N. Elyasi: None. E. Ledakaite: None. C. Arquette: None. M. Nawaz: None. S. Janusonis: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.06/A20

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant R35 NS097340
NSF Grant IOS-1853719
CIHR DFSA Grant

Title: Toll-7 acts via distinct signaling axes to promote midline crossing in *Drosophila*

Authors: *S. GAGNON¹, Y. ZANG², G. J. BASHAW¹;

¹Neurosci., Univ. of Pennsylvania, Philadelphia, PA; ²Neurosci., Columbia Univ., New York, NY

Abstract: Left-right coordination in bilaterally symmetric animals requires that commissural neurons extend their axons across the central nervous system (CNS) midline to contact contralateral targets. In flies, the guidance receptor Frazzled (Fra), like its human ortholog Deleted in Colorectal Cancer (DCC), signals through a canonical pathway to reorganize the growth cone cytoskeleton and a non-canonical pathway to regulate gene expression, together driving growth toward the midline. Elucidating the mechanisms of Fra canonical and non-canonical pathways is essential to understanding how distinct signaling events are coordinated to achieve precise neural circuit wiring. We performed a mass spectrometry screen in fly embryonic neurons and identified the toll-like receptor family member Toll-7 as a novel Fra interactor. Toll-7 can promote motor and olfactory axon targeting, but the mechanisms underlying its functions in these contexts remain undefined. Here we present evidence that Toll-7 acts both with and in parallel to Fra to promote axon growth across the midline. Using fluorescent *in situ* hybridization on *Drosophila* embryos, we show that *toll-7* is expressed in the CNS during midline crossing. Using immunostaining to assess the trajectory of a subpopulation of commissural neurons, we also reveal that *toll-7* mutant embryos display axon guidance defects that partly overlap with those of *fra* nulls, including midline crossing defects and breaks in longitudinal axon tracks. Re-expression of *toll-7* in commissural neurons using the UAS-Gal4 system rescues the crossing defects, suggesting a cell-autonomous function. Mechanistically, loss of a single copy of *toll-7* enhances the midline defects of mutants with attenuated Fra signaling, suggesting that Toll-7 acts with Fra to promote midline crossing. Supporting this, co-immunoprecipitation assays in transfected *Drosophila* S2R+ cells show that Fra and Toll-7 physically associate via their cytoplasmic domains, independently of the conserved Fra P motifs or the Toll-7 TIR domain. Notably, *fra*, *toll-7* double mutants show more severe midline defects than *fra* single mutants, suggesting that Toll-7 also acts independently of Fra at the midline. *fra* mutants lacking a single copy of the TIR domain adaptor *dSarm* also show more severe axon scaffold phenotypes, raising the possibility of a Toll-7-dSarm signaling axis acting in parallel to Fra-Toll-7. Together with future work elucidating the Fra pathway through which Toll-7 acts and the mechanisms

underlying the Fra-independent function of Toll-7, our results will shed light on a new role for Toll-7 in neuronal connectivity and uncover novel mechanisms of Fra signaling.

Disclosures: S. Gagnon: None. Y. Zang: None. G.J. Bashaw: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.07/A21

Topic: A.03. Axon and Dendrite Development

Support: NSTC Grant 111-2320-B-A49-015-MY3

Title: Non-centrosomal localization and dynactin targeting by the centrosomal protein Cep170 in neurons

Authors: S.-T. LEE¹, P.-T. CHEN¹, *E. HWANG²;

¹Natl. Yang Ming Chiao Tung Univ., Hsinchu, Taiwan; ²Inst. of Mol. Med. and Bioengineering, Natl. Yang Ming Chiao Tung Univ., Hsinchu City, Taiwan

Abstract: Cep170 is a centrosomal protein that localizes to the subdistal appendages of the mother centriole in mitotic cells. Mutations in the gene encoding Cep170 have been discovered in patients with microcephaly or lissencephaly, yet the pathological mechanism(s) that lead to the brain abnormality remain unclear. Our lab previously discovered that in addition to the centrosome, Cep170 also localizes to non-centrosomal sites in neurons. These non-centrosomal sites include an enrichment at the axon tip and the puncta along the neurite shaft. The N-terminus of Cep170 contains the forkhead-associated (FHA) domain, which is essential for its enrichment at the axon tip as well as the punctate distribution along the neurite, while the C-terminus contains microtubule-binding domains that are required for microtubule-based localization along the neurite. In addition, it is discovered that Cep170's localization at the axon tip affects the enrichment of p150Glued (a component of the dynactin complex) at the same site. We will also present data showing that the paralog Cep170b exhibits gene redundancy with Cep170. Our data identify the role of Cep170 in neuronal development and shed light on the pathological mechanism of its mutations on brain malformation.

Disclosures: S. Lee: None. P. Chen: None. E. Hwang: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.08/A22

Topic: A.03. Axon and Dendrite Development

Support: JSPS KAKENHI Grant JP24K09667
JSPS KAKENHI Grant JP22K06458
JST SPRING Grant JPMJSP2138

Title: Protein tyrosine phosphatase receptor type O regulates terminal arborization complexity of corticopontine axon collaterals

Authors: *J. LI¹, M. YASUMURA³, Y. OKA⁴, M. SATO²;

¹The Univ. of Osaka, Suita City, Osaka Prefecture, Japan; ²Dept. of Anat. and Neurosci., The Univ. of Osaka, Suita, Osaka, Japan; ³Dept. of Anat. and Neurosci., The university of Osaka, Suita, Osaka, Japan; ⁴Dept. of Anat. & Neuroscience, Grad. Sch. of Med., Osaka Univ., Osaka, Japan

Abstract: The structural complexity of axon collateral terminal arbors critically determines synaptic connectivity patterns in neural circuits. In corticospinal projections, individual axon collaterals exhibit distinct patterns of terminal arborization, ranging from sparse local branches to dense, highly complex arborizations in target regions such as the pontine nuclei, which mediate essential cerebral cortex-cerebellum connections. Despite the acknowledged functional importance of corticopontine collateral formations, the molecular mechanisms governing their developmental patterning remain largely unexplored. Here we identify protein tyrosine phosphatase receptor type O (PTPRO), a type III receptor protein tyrosine phosphatase, as a key negative regulator of corticopontine collateral terminal arborization. Using sparse labeling techniques to label the single neuron combined with *in utero* electroporation and optical tissue clearing, we visualized individual axon collateral development *in vivo* and performed knockdown experiments to assess PTPRO function. *Ptpro* knockdown specifically increased the density and spatial complexity of secondary and tertiary terminal branches within pontine nuclei without affecting the number of primary collateral branch points. This enhanced arborization was characterized by significant growth of these higher-order branches emerging from primary collateral branches, indicating that PTPRO functions to restrict terminal arbor elaboration rather than initial collateral formation. Mechanistic analysis using substrate-trapping mutant in which the key residue of the intracellular phosphatase domain was substituted and N-terminal deletion construct revealed that the intracellular phosphatase domain, rather than the extracellular domain of PTPRO, mediates the regulation of axon collateral arborization through phosphatase mechanisms. Our results establish PTPRO as a molecular brake on corticopontine terminal arborization, revealing a specific regulatory mechanism that controls synaptic connectivity at the level of axon collateral terminal complexity and providing new insights into how type III receptor protein tyrosine phosphatases shape neural circuit development through precise control of axon terminal morphology.

Disclosures: J. Li: None. M. Yasumura: None. Y. Oka: None. M. Sato: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.09/A23

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant 00011723

Title: Angiotensin AT1 Receptors Promote Expansion of Brain Presympathetic Circuit in Spontaneously Hypertensive Rats

Authors: *J.-J. ZHOU¹, S.-R. CHEN², D.-P. LI³, H.-L. PAN⁴;

¹The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX; ²Anesthesiol., UT-MD Anderson Cancer Ctr., Houston, TX; ³Med., Univ. of Missouri, Columbia, MO; ⁴Univ. Texas-MD Anderson Cancer Ctr., Houston, TX

Abstract: Overactivation of the sympathetic nervous system contributes critically to hypertension development. In spontaneously hypertensive rats (SHR), a widely used model of essential hypertension, the hypothalamic paraventricular nucleus (PVN) generates excessive sympathetic outflow and widespread vasoconstriction. Although the general circuitry of sympathetic-related neurons in the brain is known whether presympathetic neuronal connectivity is altered in hypertension remains elusive. Here, we used pseudorabies virus (PRV)-152, a transsynaptic retrograde tracer, to quantify presympathetic neuronal connectivity in SHR. PRV-152 injected into the adrenal gland labeled substantially more neurons in the PVN and rostral ventrolateral medulla (RVLM) in adult SHR than in normotensive Wistar-Kyoto rats (WKY), with no difference in the spinal intermediolateral column (IML). In contrast, young, prehypertensive SHR showed similar labeling to WKY in these brain regions. PRV-152 injection into the brown adipose tissue resulted in comparable neuronal labeling in the PVN, RVLM, and IML in adult SHR and WKY. Remarkably, long-term treatment with losartan, an angiotensin AT1 receptor antagonist, initiated at a young age, diminished both the age-dependent rise in blood pressure and the increased neuronal labeling in the PVN and RVLM of SHR. In WKY, losartan had no significant effect on blood pressure or PRV-152 labeling in these brain regions. Our findings reveal that SHR exhibit increased, organ-specific connectivity of presympathetic neurons in the hypothalamus and brainstem during hypertension progression. The enhanced connectivity is driven by age-dependent activation of endogenous AT1 receptors, supporting elevated sympathetic vasomotor tone in neurogenic hypertension.

Disclosures: J. Zhou: None. S. Chen: None. D. Li: None. H. Pan: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.10/A24

Topic: A.03. Axon and Dendrite Development

Support: R01 HD105946
IOS-1853719

Title: Ndfip Intracellular Trafficking is Required for Lysosomal Degradation of Robo1 During Commissure Formation

Authors: *M. HALE, C. POTTER, G. J. BASHAW;
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: During mammalian embryonic spinal cord development, commissural neurons (CN) extend their axons across the floorplate (FP), forming commissures that are important for coordination of motor and sensory functions. Growth cones of commissural axons (CA) contain membrane-bound receptors that interact with ligands secreted from the FP and ventricular zone, resulting in either attraction or repulsion. Roundabout (Robo1) mediates repulsion via interactions with its ligand Slit. In pre-crossing axons, Robo1 is downregulated to impede Slit-induced repulsion and permit CA entry into the FP. In contrast, during crossing and post-crossing, surface expression of Robo1 increases, inducing Slit-mediated repulsion. This allows CAs to exit the FP and prevents their re-entry. A proposed mechanism for the spatiotemporal regulation of Robo1 during CA guidance in the mammalian spinal cord is through the adaptor function of the late endosomal proteins Nedd4 family interacting proteins 1 and 2 (Ndfip1/2). Ndfips interact with HECT Family E3 Ubiquitin Ligases (E3 ligases) to facilitate Robo1 ubiquitylation and subsequent endo-lysosomal degradation. Interestingly, knockout (KO) of Ndfip1/2 in E11.5 mice results in increased expression of Robo1 in pre-crossing CAs, and ventral commissure thinning. Blinded immunofluorescence experiments find that overexpression of Ndfip1 in dissociated E12.5 CNs decreases Slit response, but that abrogation is not observed with overexpression of Ndfip1 proteins that cannot interact with E3 ligases (Ndfip1^{PY}) (n=750 neurons). This data, combined with blinded quantification of commissure thickness in E11.5 Wildtype, Ndfip1 conditional KO, and Ndfip1;Robo1/2 triple KO (n=2,3,4), suggests that Ndfip1 modulates Slit-induced CA repulsion in a Robo1-dependent manner. To determine the requirement of Ndfip1 late endosomal localization for this function, we generated Ndfip1 constructs with point-mutations in candidate domains. Overexpressing these constructs in dissociated E12.5 CNs altered colocalization with late endosomal marker Rab7 (n=354 neurons), increased Robo1 expression at the growth cone (n=350 neurons) and resulted in Slit responses like that of Ndfip1^{PY} (n=354). These data taken together suggest that endosomal localization of Ndfip1 may be important for its role in downregulating Robo1 and inhibiting CA repulsion during commissure formation. This and future work may elucidate mechanisms of Ndfip1 trafficking, inform potential subcellular locations of cargo interactions, and further the mechanistic understanding of Ndfip1-mediated regulation of commissural axon guidance in the spinal cord.

Disclosures: M. Hale: None. C. Potter: None. G.J. Bashaw: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.11/A25

Topic: A.03. Axon and Dendrite Development

Support: RS-2023-00275939
RS-2021-NR056908
HR21C0198

Title: Exoc4 gene knockdown impairs neurite outgrowth by disrupting cytoskeletal dynamics

Authors: *J. KANG¹, S. CHOI², H. PARK², D. YOO², J. KIM³, A. SADRA², S.-O. HUH²;
¹Dept. of Pharmacol., Hallym Univ., chuncheon, Korea, Republic of; ²Dept. of Pharmacol., Hallym Univ., Chuncheon, Korea, Republic of; ³Dept. of Life Sci., Ewha Womans Univ., Seoul, Korea, Republic of

Abstract: Aberrant neuronal migration and disorganized axonal patterning have been increasingly recognized as key pathological features contributing to the etiology of neurodevelopmental disorders, including autism spectrum disorder (ASD). Genetic studies have identified a broad spectrum of mutations in individuals with ASD, underscoring the involvement of diverse molecular pathways. In this study, we identify Exocyst Complex Component 4 (EXOC4) as a critical regulator of neuronal migration and axonal development during embryonic brain development in mice. Immunofluorescence analysis revealed that EXOC4 is highly expressed in developing cortical neurons, with prominent localization in the neuronal soma. To investigate its functional role, we employed in utero electroporation (IUE) to knock down EXOC4 expression via RNA interference. EXOC4 silencing resulted in significant impairments in radial migration and corpus callosum axon elongation during corticogenesis. In vitro, primary cortical neurons with EXOC4 depletion exhibited reduced dendritic complexity and shortened axonal projections. These findings collectively demonstrate that EXOC4 plays an essential role in orchestrating the neuronal architecture of the developing neocortex and may contribute to the pathophysiology of ASD-related cortical malformations.

Disclosures: J. Kang: None. S. Choi: None. H. Park: None. D. Yoo: None. J. Kim: None. A. Sadra: None. S. Huh: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.12/A26

Topic: A.03. Axon and Dendrite Development

Support: Japan Society for the Promotion of Science 23K06328

Title: Immunohistochemical analysis on the role of Plexin-A3 for Erk signaling in SOX9-positive glial cells translocating to the indusium griseum during corpus callosum development

Authors: *K. YUKAWA¹, M. HOSSAIN¹, S. SASAKI¹, T. TSUZUKI¹, I. TAKAHASHI¹, T. KAWASAKI², T. NEGISHI¹;

¹Meijo Univ., Nagoya, Japan; ²Brain function, Natl. Inst. of Genet., Mishima-Shi, Japan

Abstract: The corpus callosum (CC) is the largest commissure that links cerebral hemispheres. Plexin-A3 (PlxnA3) is a signal-transducing transmembrane receptor for semaphorins, a family of axon guidance molecules. *PlxnA3* is expressed in the cingulate cortex from which callosal pioneer axons extend towards the midline for CC development. However, the role of PlxnA3 in CC development remains unclear. The guidepost structures like the glial wedge (GW) in the ventricular zone, indusium griseum glia (IGG) and midline zipper (MZ) lead callosal axons across the midline through the action of axon guidance molecules. Somas of radial glial cells (RGC) move through the somal translocation from the GW to the indusium griseum (IG) at the pial surface and differentiate into mature astrocytes, leading to the formation of IGG. To disclose the role of PlxnA3 in the glial translocation and CC development, immunohistochemical analyses were performed. The midline crossing of neuropilin1-expressing callosal pioneer axons at embryonic day 17.5 (E17.5) was significantly impaired in *PlxnA3* KO mice compared with wild type (WT) mice under a genetic background of BALB/cA. The expression of PlxnA3 was detected in GFAP-positive astrocytes residing in the IG and MZ at E17.5. Both GFAP-positive cells and Sox9-positive cells in the IG region of *PlxnA3* KO brains were significantly fewer than those of WT. *Slit2* mRNAs were scarcely localized in the IG region in *PlxnA3* KO brains at E17.5 under the condition in which *Slit2* mRNAs were detected in GFAP-positive cells in the IG and MZ in WT. FGF signal which activates Erk is essential for the somal translocation of RGC. In the study to examine the role of PlxnA3 on the Erk signaling, both the SOX9/pERK double positive cells and the percentage of pErk-positive cells in the Sox9-positive cells in *PlxnA3* KO mice at E17.5 significantly reduced in the path from the GW to the IG as compared with WT. Thus, it is suggested that Erk signaling in SOX9-positive cells during the somal translocation significantly decreased in PlxnA3-deficient embryos than in WT. Accordingly, both PlxnA3-mediated signal and FGF signal may converge into the activation of Erk in the Sox9-positive glial cells moving toward the IG.

Disclosures: K. Yukawa: None. M. Hossain: None. S. Sasaki: None. T. Tsuzuki: None. I. Takahashi: None. T. Kawasaki: None. T. Negishi: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.13/A27

Topic: A.03. Axon and Dendrite Development

Support: Taiwan's National Science and Technology Council, MOST-111-2314-B-007-002-MY3

Title: Piezo1-mediated suppression of magnetically guided axon outgrowth in hipsc-derived rgcs

Authors: *T.-C. YANG¹, C.-C. CHIAO²;

¹Taipei Med. Univ., Taipei, Taiwan; ²Dept. of Life Sci., Natl. Tsing Hua Univ., Hsinchu, Taiwan

Abstract: Axon regeneration in retinal ganglion cells (RGCs) remains a critical challenge for vision restoration. Here, we engineered a nanotechnology-based platform to guide axon outgrowth in human induced pluripotent stem cell (hiPSC)-derived RGCs using Magnetic Neural Axon Vectors (MagNAVs). These raspberry-like iron oxide nanoparticles were internalized into RGCs and exposed to an external magnetic field (MF), resulting in enhanced neurite alignment and elongation along the MF vector. Immunostaining and functional assays revealed that the mechanosensitive ion channel PIEZO1 is highly expressed in hiPSC-RGCs and functions as a negative regulator of neurite outgrowth. Pharmacological inhibition of PIEZO1 using Dooku1 significantly increased neurite length, particularly under magnetic stimulation, whereas PIEZO1 activation with Yoda1 impaired this response. Two-photon calcium imaging further demonstrated that PIEZO1 modulates compartment-specific spontaneous calcium transients, suppressing axonal calcium signaling under mechanical stimulation. These findings highlight a previously uncharacterized mechanosensory axis that governs RGC axon behavior, offering a novel approach to enhance axon regeneration via PIEZO1 modulation and magnetic force-guided nanotechnology.

Disclosures: T. Yang: None. C. Chiao: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.14/A28

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant 5R01NS134969
Shurl and Kay Curci Foundation Grant
Stanford Maternal and Child Health Research Institute Faculty Scholar Award

Title: A eutherian specific microRNA cluster regulates netrin pathway genes to control corticospinal projection development

Authors: P. SURENDRAN, V. SITHTHANANDAN, *S. A. THARIN;
Stanford Univ., Palo Alto, CA

Abstract: The mammalian CNS contains distinct projections from the cerebral cortex, essential for motor and cognitive function, including the corticospinal tract and corpus callosum. Interestingly, the neurons giving rise to these two projections, corticospinal motor neurons (CSMN) and callosal projection neurons (CPN), originate from the same progenitors although they exhibit strikingly different projections and functions. We have identified a cluster of microRNAs that are selectively expressed by CSMN vs. CPN during their development. This microRNA cluster, like the fully elaborated corticospinal tract and the corpus callosum, is unique to placental mammals. Our bioinformatic analyses predict that multiple microRNAs from this cluster, located at 12qF1 in the mouse, regulate axonal guidance genes in the netrin pathway including *Unc5c*, *Neol1*, and netrin interacting protein LMO4. Here we show that one 12qF1 microRNA, miR382-3p, represses an *Unc5c* reporter in luciferase assays. In primary culture, miR-382-3p overexpression/gain-of-function (GOF) represses netrin-1-mediated corticospinal axon outgrowth. Interestingly, miR-382-3p GOF does not affect corticospinal fate in primary culture, suggesting that miR-382-3p shapes corticospinal identity by controlling CSMN axon projections rather than transcription factor expression and/or fate. We are currently undertaking targeted miR-eCLIP in corticospinal motor neurons to identify and validate additional 12qF1 microRNA::netrin pathway interactions. Our results suggest a molecular mechanism whereby a placental mammal-specific microRNA cluster could control the development of two major projections that underpin complex mammalian behaviors.

Disclosures: P. Surendran: None. V. Siththanandan: None. S.A. Tharin: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.15/A29

Topic: A.03. Axon and Dendrite Development

Title: Miro1-mediated mitochondrial dynamics during axon growth and development

Authors: J. AFSAR-KESHMIRI, *A. K. MYERS;
Hamilton Col., Clinton, NY

Abstract: During development, fast transport along microtubules allows mitochondria to distribute to areas that require high energy to forge neural networks such as synapses, active growth cones, and axon branch sites. Mitochondrial Rho GTPase 1 (MIRO1) is a motor-associated protein anchored in the outer mitochondrial membrane that functions to bind

mitochondria to molecular motors enabling their calcium (Ca²⁺)-dependent movement along microtubules. Previous research suggests that MIRO1 plays a role in developing and regenerating axons, influencing axonal branching and growth. Disruptions to MIRO1 function have been implicated in neurodegenerative diseases such as amyotrophic lateral sclerosis. Our data suggest that *Miro1* can also play a role in anxiety-like behavior when ablated from excitatory neurons during development. Observed structural brain changes include decreased cortical and hippocampal volume as well as a reduction in critical axon pathways such as the corpus callosum. In this study, we continue to examine *Miro1*-ablated excitatory neurons, their mitochondrial distribution, and circuitry. We investigate potential binding partners of MIRO1 that influence axonal growth and contribute to the aberrant behaviors we have observed in *Miro1*-conditionally ablated mice. These experiments further contribute to our understanding of *Miro1*'s role in axonal development and neurological disease.

Disclosures: J. Afsar-Keshmiri: None. A.K. Myers: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.16/A30

Topic: A.03. Axon and Dendrite Development

Support: NIH R35 NS097340

Title: Nuclear export as a regulator of the Fra/Dcc transcriptional switch underlying midline circuit assembly

Authors: *D. A. JIMENEZ¹, Y. ZANG², G. J. BASHAW¹;

¹Neurosci., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA; ²Neurosci., Columbia Univ., New York, NY

Abstract: Ensuring neural circuits assemble properly is essential for establishing motor, sensory, and cognitive functions. However, how the transcriptional programs that dictate circuit assembly are regulated is incompletely understood. In bilaterally symmetric organisms, commissural neurons in the central nervous system project their axons across the embryonic midline in a precisely timed and conserved process to make synaptic connections with contralateral targets. Canonically, midline crossing is mediated by cytoskeletal remodeling downstream of interactions between transmembrane axon guidance receptors (AGRs) and attractive/repulsive cues secreted from the midline. Recently, we identified a non-canonical role for AGRs as regulators of gene expression during circuit assembly. In *Drosophila*, the Frazzled (Fra) AGR releases its intracellular domain (ICD) to induce transcription of *commissureless* (*comm*), a negative regulator of repulsive signaling by the Robo1 AGR. In an unbiased mass spectrometry screen, we identified Embargoed (Emb), a nuclear export factor, as an interactor of Fra. Emb,

orthologous to mammalian CRM1, shuttles cargo by interacting with nuclear export signals (NESs). Previously, we showed that the Fra ICD exits the nucleus in an NES-dependent manner. Here, we explore Emb as a candidate regulator of Fra non-canonical signaling. Using the *Gal4-UAS* system to genetically label *eagle+* (EW) neurons, a population of embryonic commissural neurons in the *Drosophila* ventral nerve cord, we examined whether loss of Emb can influence midline crossing. Using a newly generated *emb* CRISPR knock-out (KO) line, we found that loss of Emb led to a significant increase in EW neuron midline projection defects (wildtype: mean 7% SD $\pm$ 7%; KO: 44% $\pm$ 11% $p < 0.001$). Projection defects resembled those observed in embryos deficient in other regulators of Fra non-canonical signaling, suggesting a regulatory role for Emb in axon guidance. Ongoing work aims to investigate genetic interactions between *emb* and *fra*. Specifically, we will examine Emb's role in regulating the Fra ICD's localization *in vivo* by overexpressing a Myc-tagged ICD in *eagle+* neurons in wildtype and *emb* KO backgrounds. We will also use fluorescence *in situ* hybridization using a *comm* probe to test Emb's role in regulating Fra's transcriptional outputs. Lastly, we will use a *fra* partial loss of function background, in which EW neurons display moderate defects in midline crossing, to test whether loss of Emb can rescue midline crossing defects. Rescue would strongly support the model in which Emb acts in the Fra pathway to regulate midline crossing.

Disclosures: D.A. Jimenez: None. Y. Zang: None. G.J. Bashaw: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.17/A31

Topic: A.03. Axon and Dendrite Development

Support: Adelson Medical Research Foundation AMRF_81884

Title: Spatial multiomics profiling of human neural repair mechanisms

Authors: H. XU¹, A. G. WILCOX², R. WONG², G. SHIN², A. PATOWARY², *S. LYMER³, T. WOLF³, J. ZHAO³, D. H. GESCHWIND²;

¹Neurol., Univ. of Chicago, Los angeles, CA; ²Univ. of California Los Angeles, Los Angeles, CA; ³Element Biosci., San Diego, CA

Abstract: How human neurons regenerate after injury—and how this process can be enhanced—remains a key question in the field. While animal models provide valuable insights, the molecular pathways that control regeneration in human neurons are still incompletely understood. In this study, we used an *in vitro* human sensory cell regeneration model, and applied a novel technology - the AVITI24™ Teton™ CytoProfiling spatial multiomics platform to capture spatially resolved gene expression (n = 350 genes) and protein (n = 50 proteins) changes across the functional regenerating neuron subtypes (n = 3 replicates, ~2.5k

cells/replicate). In addition, we applied growth-promoting compounds that we previously screened in our lab to explore how different pro-regenerative drugs shape the molecular landscape of regeneration. Our preliminary data revealed that distinct drugs drive unique patterns of axon growth, linked to activation of pathways controlling axon guidance, cytoskeletal remodeling, lipid metabolism, cell adhesion, and neuronal stress responses. In summary, our work represents the first application of spatial-multiomics technology to systematically profile the molecular mechanisms underlying drug-enhanced regeneration in human sensory neurons. By linking molecular pathways to functional outcomes, this approach offers a powerful framework for identifying molecular mechanisms to promote neural repair in human disease and injury.

Disclosures: **H. Xu:** None. **A.G. Wilcox:** None. **R. Wong:** None. **G. Shin:** None. **A. Patowary:** None. **S. Lymer:** A. Employment/Salary (full or part-time): Element Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Element Biosciences. **T. Wolf:** A. Employment/Salary (full or part-time): Element Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Element Biosciences. **J. Zhao:** A. Employment/Salary (full or part-time): Element Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Element Biosciences. **D.H. Geschwind:** None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.18/A32

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant 5R01NS113314-04
NIH Grant 1R21NS125419-01

Title: Erbb ligand-induced invadosome formation and function in *Xenopus* spinal neurons

Authors: ***T. LOUGHERY**¹, T. M. GOMEZ²;

¹Univ. of Wisconsin- Madison, Madison, WI; ²Dept of Neurosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: During development, motor neuron (MN) axons must navigate out of the central nervous system (CNS) and travel through diverse tissue environments to reach their peripheral targets. To exit the spinal cord, growth cones, the sensory-motile tips of growing axons, respond to guidance cues in the environment to promote crossing the dense basal lamina surrounding the developing spinal cord. We showed that developing MN axons and growth cones form F-actin-rich invadosomes *in vitro* and *in vivo* that allow them to exit the spinal cord. Invadosomes are

protrusions that recruit and release matrix metalloproteases (MMPs) to locally remodel the extracellular matrix, allowing cells to migrate across tissue barriers. While well-studied in metastatic cancer cells and immune cells, invadosomes in growth cones are still poorly understood. In this study, we found that epidermal growth factor (EGF) receptor, or ErbB, ligands, EGF and neuregulin 1 (Nrg1) induce invadosome formation in *Xenopus* spinal neurons via kinase signaling. Using *in vitro* assays, we find that EGF ligands activate Src signaling pathways, and increase gelatin degradation in growth cones, indicating increased MMP activity. Using wholemount labeling techniques including HCR RNA-FISH and IHC, we find that ErbB4, a member of the EGF receptor family, is expressed in MNs during the stage of axon exiting, while ligands Nrg1 and EGF are expressed in spinal neurons as well as surrounding tissues. We have also characterized expression of other invadosomal markers, like scaffolding protein Tks5 and MMP14 *in vivo*. Ongoing experiments explore overexpression and CRISPR/Cas9-mediated knockout of relevant members and the effects on neurite outgrowth and matrix degradation *in vitro*, and axon exiting *in vivo*. Understanding the mechanisms utilized by developing spinal neurons to form these invasive structures that allow them to exit the spinal cord is essential for informing therapeutic regeneration research of these same populations that may be lost due spinal cord injury or diseases like ALS.

Disclosures: T. Loughery: None. T.M. Gomez: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.19/A33

Topic: A.03. Axon and Dendrite Development

Support: McPherson Eye Research Institute 2024 Kenzi Valentyn Vision Research Grant
McPherson Retinal Research Foundation Award
NIH Grant 1R21EY035831-01

Title: Dissecting the role of extracellular matrix proteins, cell adhesion molecules, and cytoskeletal regulators in age-dependent loss of human photoreceptor terminal motility

Authors: *M. DILLERUD¹, A. PIER⁴, S. K. REMPEL², D. M. GAMM⁵, T. M. GOMEZ³;
¹Neurosci., ³Dept of Neurosci., ²Univ. of Wisconsin - Madison, Madison, WI; ⁴Neurosci., Univ. of Wisconsin - Madison Neurosci. Training Program, Madison, WI; ⁵Ophthalmology and Visual Sci., Univ. of Wisconsin, Madison, WI

Abstract: Diseases of the retina in which photoreceptors (PRs) are lost, such as age-related macular degeneration (AMD), can severely impair a patient's vision and, consequently, their quality of life. Therefore, with an aging population, finding effective therapies for diseases such

as AMD has become increasingly important. The transplantation of PRs, the primary sensory cell of the retina, represents a promising treatment. One roadblock in PR transplantation studies is the inefficient integration of transplanted PRs into existing retinal circuits. As our understanding of PR axon extension is limited, this study aims to improve our basic understanding of PR motility mechanisms that are essential for successfully integrating PRs during development. Recent research from my laboratory demonstrated that human pluripotent stem cell-derived PRs lose the capacity for autonomous growth cone-mediated extension between day 50 (d50) and day 100 (d100) of differentiation. Bulk RNA sequencing data collected from fluorescence-activated cell-sorted d50 and d100 stem cell-derived PRs identified several genes that were down-regulated concurrently with the loss of autonomous axon extension. These genes included extracellular matrix (ECM) proteins and their cognate receptors, cell adhesion molecules, and proteins that directly regulate the cytoskeleton. Using quantitative immunostaining techniques, I examined the distribution and expression levels of several of these key motility-associated proteins within human PRs *in vitro* and within retinal organoids (ROs). Additionally, I have investigated the effect of ECM substrata on receptor expression, distribution, and process extension of PRs cultured onto a variety of ECM proteins. Consistent with transcriptomic data, I find that the expression levels of some ECM receptors are significantly reduced in mature PR terminals on all tested substrata, suggesting that loss of these receptors may be responsible for age-related loss of PR terminal mobility. Additionally, some receptors show different expression levels depending on both PR age and culture substrata, suggesting that ECM proteins may influence expression of motility-associated genes. These results provide us with insight into potential mechanisms essential to PR axon extension and integration, as well as possible motility-associated targets to re-express in d100 PRs to improve autonomous axon extension.

Disclosures: M. Dillerud: None. A. Pier: None. S.K. Rempel: None. D.M. Gamm: Other; Co-founder of Opsis Therapeutics. T.M. Gomez: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.20/A34

Topic: A.03. Axon and Dendrite Development

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

Title: Defining the role of tubulin isoforms during AIS assembly

Authors: *Y. XING¹, M. N. RASBAND²;

¹Neurosci., Baylor Col. of Med., HOUSTON, TX; ²Neurosci., Baylor Col. of Med. Dept. of Neurosci., Houston, TX

Abstract: Microtubules (MTs) are essential cytoskeletal components in neurons, playing crucial roles in maintaining neuronal integrity and supporting various subcellular functions. Two factors are thought to influence the biochemical properties of MT: 1) posttranslational modifications (PTMs) and 2) the specific tubulin isoforms incorporated into microtubules. These are collectively defined as the "tubulin code." While most tubulin PTMs are well studied, little is known about the differential distribution and function of tubulin isoforms despite a growing number of reports of tubulin mutations associated with neurological diseases. Tubulin isoforms are predicted to have unique localizations and perform different functions in neurons due to their different biochemical properties. One such compartment is the axon initial segment (AIS) where MTs are hyper stable and form fasciculated structures. Thus, I hypothesize that specific tubulin isoforms are enriched at the AIS, and they support the integrity and the function of the AIS. Using a CRISPR-KI technology, I found eight tubulin isoforms expressed in cultured neurons. None are exclusively enriched at the AIS. Although not enriched at the AIS, they are detergent resistant at the AIS, which suggests that they may serve key roles at the AIS. Nevertheless, these results indicate that the specific tubulin isoform may not be critical for AIS. To further define if tubulin isoforms play specific roles in neurons, I knocked out alpha and beta tubulin isoforms in cultured neurons and found that triple knockout of the major tubulin isoforms (*Tubal1a*, *Tubal1b*, *Tubal1c*) results in disassembly of AIS while single knockout of other isoforms has no obvious effect on AIS integrity, suggesting functional redundancy among tubulin isoforms. Together, these data challenge our initial hypothesis and suggest that the tubulin isoform is not a key determinant of AIS structure and function.

Disclosures: Y. Xing: None. M.N. Rasband: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.21/A35

Topic: A.03. Axon and Dendrite Development

Support: R01HD094809-06
R21HD106032-01

Title: Iron is required for proper neuronal axon specification and growth

Authors: J. CROSBY¹, *T. R. MONKO¹, J. BAILARD¹, S. OSTERGREN², T. W. BASTIAN¹;
¹Pediatrics, Univ. of Minnesota, Minneapolis, MN; ²NIH, Bethesda, MD

Abstract: Gestational and perinatal iron deficiency is one of the most common insults to brain development, yet there is a paucity of knowledge about iron requirements during the earliest periods of neuronal development from axon specification and elongation to pathfinding and synapse formation. Developing neurons have high metabolic requirements to facilitate

cytoskeletal rearrangement and cellular transport, and iron homeostasis has been implicated in mitochondrial transport and dendritic arborization in later neuronal development. We hypothesized that sufficient iron availability is essential during the earliest stages of neuronal development for proper regulation of axon specification, elongation, and branching. To study the earliest stages of axon growth, we developed a novel model to investigate axon development using primary neurons cultured from mid-embryonic mouse cortex. Neurons were treated with iron chelators (iron depletion condition) or vehicle (iron sufficient) beginning at 2 hours in culture. Neuronal iron status, morphology, and axon growth were assessed from 3 to 108 HIC using live cell dyes and immunocytochemistry, and quantified using our open source bio-image analysis pipeline available as napari-ndev. In young primary neurons, iron availability increased iron storage (ferritin) and cycling (NCOA4; nuclear receptor coactivator 4) proteins over time. Sufficient iron was necessary for proper specification and elongation of a single axon, as identified by LKB1 (liver kinase B1) and SMI-312 (phosphorylated neurofilament epitopes). Iron depleted neurons either formed exuberant neurites and branches at the cost of axon specification or invested primarily in elongation of a single neurite at the cost of other neurite growth. These findings suggest that young neurons tightly regulate iron homeostasis during embryonic brain development. Iron plays an essential role in early axon development by promoting axon specification and balanced neurite growth. Understanding the roles of iron during embryonic brain development is crucial for revealing unifying mechanisms underlying neuronal development during iron deficiency.

Disclosures: J. Crosby: None. T.R. Monko: None. J. Bailard: None. S. Ostergren: None. T.W. Bastian: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.22/A36

Topic: A.07. Development of Neural Systems

Title: An emergence model that accounts for both precise and variable neurite patterning across individuals derived from multiple C. elegans electron microscopy reconstructions

Authors: *C. BRITTIN;

Developmental Biol., Mem. Sloan Kettering Cancer Ctr., New York, NY

Abstract: High-resolution neuronal connectivity ("connectome") data detail at single-axon resolution how hundreds to hundreds of thousands of neurons make precise pairwise contacts within dense tissue. A casualty of these information rich datasets is that distilling simple models which explain how complex organization emerges from early developmental patterns is challenging. An open question is whether the collectively precise patterning of individual axons characterized in these datasets depends on equally elaborate molecular targets, or if such precise

patterning can emerge through target independent mechanisms. To address this question, I constructed a minimal tissue morphogenesis model that quantitatively accounts for electron micrograph (EM) derived patterning of precise and variable pairwise neurite contacts in the main *C. elegans* neuropil. I show that 9 previously published volumetrically reconstructed EM datasets from individual worms that span all larval developmental stages consistently exhibit two key systems-level features: bimodal pairwise contact reproducibility and spatial domain organization. Bimodal reproducibility indicates that most pairwise neurite contacts are either stereotypically observed in all individuals or in only one individual. Spatial domain organization indicates that neurites stereotypically cluster into the same patterns across all individuals. To explain the emergence of these systems-level features, I constructed a simple pioneer-follower model that mimics key features of early *C. elegans* nerve ring development. To test the model, I engineered an *in silico* agent based simulator of 3D nerve ring innervation. The simulator demonstrates that bimodal reproducibility and spatial domain organization spontaneously emerge when modest conditions relating to tissue geometry, pioneer scaffold size, molecular specificity and spatial proximity of pioneers and followers are satisfied. Notably, the simulator makes two key predictions regarding specificity and spatial proximity that help explain why nerve ring organization is not easily explained by recent scRNA-seq analysis. Finally, the simulator accounts for why nerve ring development is robust to empirical cell ablations and makes developmental predictions regarding potential surface protein knockouts. Because the underlying model makes no assumptions about pairwise target specification, the simulator results demonstrate how precise and variable pairwise patterning of individual neurites can emerge through target independent mechanisms without requiring an elaborate molecular code to specify neurite positions.

Disclosures: C. Brittin: None.

Poster

PSTR002: Decoding Axonal Navigation: Molecular and Cellular Insights From Invertebrates to Mammals

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR002.23/A37

Topic: A.03. Axon and Dendrite Development

Title: Lrrn-mediated synaptic specificity drives visual circuit assembly for brightness and contrast detection

Authors: *E. PUTTI¹, G. FAINI², T. DANG¹, J. H. SAVALIYA³, K. DUROURE¹, A. BAHL⁴, F. ENGERT⁵, J. W. LICHTMAN⁶, J. BOULANGER-WEILL⁷, F. DEL BENE¹, S. ALBADRI⁸;
¹Inst. de la Vision, Paris, France; ²Vision Inst., Paris, France; ³Univ. of Regina, Regina, SK, Canada; ⁴Univ. of Konstanz, Konstanz, ; ⁵Harvard Univ., Cambridge, MA, ; ⁶Harvard Univ., Cambridge, MA; ⁷Harvard Univ. and Fondation Voir et Entendre, Paris, ; ⁸Vision Institute, Sorbonne Univ., Paris.

Abstract: Brightness and contrast are fundamental features of vision, crucial for object detection, environmental navigation, and feeding. Here, we identify a brightness- and contrast-processing circuit in the zebrafish visual system and uncover the role of Leucine-rich repeat neuronal (Lrn) cell adhesion molecules (CAMs) in regulating its assembly. We show that deep-projecting retinal ganglion cells serve as the first synaptic relay to the brain, requiring Lrn2 and Lrn3a for precise axonal targeting and connectivity within the optic tectum. Using a novel reporter line, we achieved high-resolution mapping of this previously under-characterized vertebrate visual circuit. Genetic disruption of Lrn CAMs leads to disorganization of the circuit and impairments in contrast sensitivity, resulting in deficits in visually guided behavior. Additionally, ultrastructural circuit reconstruction and functional imaging analysis identified both its synaptic partners and revealed its critical role in luminance processing. These studies define a core visual processing pathway and establish Lrn CAMs as essential molecular drivers of its assembly.

Disclosures: E. Putti: None. G. Faini: None. T. Dang: None. J.H. Savaliya: None. K. Durore: None. A. Bahl: None. F. Engert: None. J.W. Lichtman: None. J. Boulanger-Weill: None. F. Del Bene: None. S. Albadri: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.01/A38

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NINDS IRP 1ZIAN009424
NINDS IRP 1ZIAN009416

Title: Neuregulin1 signaling from membrane-to-nucleus sculpts neural diversity in cell types and circuit connectivity.

Authors: *P. RAJEBHOSALE¹, L. JIANG², N. S. DESAI³, L. W. ROLE⁴, D. A. TALMAGE⁵; ²NINDS, ¹NIH/ NINDS, Bethesda, MD; ³Circuits, Synapses, and Mol. Signaling Section, ⁴NINDS, ⁵NINDS, Bethesda, MD

Abstract: The mammalian brain is among the most heterogeneous organs, boasting the greatest transcriptionally defined diversity of cell types. Intriguingly, this diversity increases in complexity during postnatal development, suggesting that developing synapses and experience-dependent mechanisms might shape the diversity observed in the adult brain. In the mouse dentate gyrus (DG), we recently uncovered a critical role for membrane-to-nucleus signaling by a cysteine-rich domain-containing isoform of Neuregulin1 (CRD-Nrg1) in preserving neuronal subtype diversity during postnatal maturation. CRD-Nrg1 is an axonal presynaptic membrane protein that, upon synaptogenic interactions or activity, can be processed by gamma secretase to yield a free cytoplasmic intracellular domain (ICD). The free Nrg1 ICD can traffic to the

nucleus, where it plays a role in transcriptional regulation. A missense mutation in Nrg1 (Val321Leu; V321L), associated with psychosis, disrupts this membrane-to-nucleus signaling and leads to a striking loss of subtype-specific neuronal features, including alterations in morphology, physiology, and transcriptional identity. These changes parallel those seen in various neuropsychiatric models and postmortem human brains from individuals with schizophrenia, Alzheimer's disease, and others, suggesting that loss of neural diversity may reduce adaptive capacity and predispose circuits to dysfunction. We now show that the V321L mutation also alters long-range connectivity between the anterior cingulate cortex (ACC) and basolateral amygdala (BLA). In wild-type mice, DARPP32+ neurons in the BLA selectively respond to ACC input; this specificity is altered in V321L mutants, which also exhibit broader BLA activation in response to aversive stimuli, potentially reflecting disrupted ACC-to-BLA targeting and local circuit remodeling. We found that CRD-Nrg1 is highly expressed in ACC projection neurons but minimally expressed in the BLA. Single-cell RNA sequencing of the ACC revealed subtle transcriptional changes in excitatory neurons, but more robust shifts in microglial gene expression and morphology. These findings raise the possibility that disrupted CRD-Nrg1 signaling reprograms local cellular states, including non-neuronal populations, which in turn may alter circuit output. We are now investigating whether these microglial changes affect synaptic or intrinsic properties of ACC neurons and using axonal proteomics to identify molecular mediators of altered BLA targeting.

Disclosures: P. Rajebhosale: None. L. Jiang: None. N.S. Desai: None. L.W. Role: None. D.A. Talmage: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.02/A39

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NINDS IRP

Title: A ventral pallidal to basolateral amygdala cholinergic circuit mediates valence encoding

Authors: *R. KIM, L. JIANG, L. W. ROLE, D. A. TALMAGE;
NIH/NINDS, Bethesda, MD

Abstract: Proper valence encoding is critical for survival. The ability to recognize positive valence stimuli as appetitive and negative valence stimuli as aversive is necessary for appropriate behavioral responses (i.e., approach appetitive stimuli and avoid aversive stimuli). Previously we identified two distinct populations of ventral pallidal (VP) cholinergic neurons that differentially encode valence and play opposing roles in approach vs. avoidance behaviors. The primary output target of VP cholinergic neurons is the basolateral amygdala (BLA). The BLA also is involved in valence encoding. Whether valence encoding VP cholinergic neurons form anatomical and/or

functional connections with valence encoding BLA neurons remains unknown. To determine the relationship between VP cholinergic and BLA neurons in valence encoding, we utilized longitudinal single-cell calcium imaging of BLA neurons during exposure to a positive valence, appetitive odor (2-phenylethanol) and a negative valence, aversive (mountain lion urine) odor, with and without optogenetic stimulation of VP cholinergic terminals in the BLA.

Approximately equal numbers of BLA neurons were activated by odors of each valence (44% positive valence, 43% negative valence). Pairing odor delivery with optogenetic stimulation of VP cholinergic terminals in the BLA enhanced the calcium activity of negative valence but not positive valence BLA neurons. Ongoing studies will determine how VP cholinergic signaling alters the activity of BLA neurons. First, we are using whole cell patch clamp electrophysiology to monitor the activity of BLA interneurons (labeled with AAV-DLX-GFP) and BLA pyramidal neurons during optogenetic stimulation of VP cholinergic terminals. Second, we developed an activity- and cre-dependent viral tool (ADCD-oCHIEF) to specifically label positive vs. negative valence VP cholinergic neurons and their terminals. Using electrophysiology and high-resolution imaging, we will specifically target VP positive vs. negative valence VP cholinergic neurons and map their functional and anatomical connections with valence-encoding BLA neurons.

Disclosures: R. Kim: None. L. Jiang: None. L.W. Role: None. D.A. Talmage: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.03/A40

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Key-Area Research and Development Program of Guangdong Province Grant 2023B0303010001
National Natural Science Foundation of China (NNSFC) Grant 32471250
NNSFC Grant 82022018
NNSFC Grant 32070958
NNSFC Grant 82161138025
NNSFC Grant 32471262
NNSFC Grant 92269102

Title: Structural basis of calcium-dependent C1ql/BAI assemblies in synaptic connectivity

Authors: *Y. HAN^{1,2}, B. ZHANG³;

¹Peking Univ. Shenzhen Grad. Sch., Shenzhen, China; ²Inst. of Neurolog. and Psychiatric Disorders, Shenzhen Bay Lab., Shenzhen, China; ³Sch. of Chem. biology and Biotech., Peking Univ. Shenzhen graduate school, Shenzhen, China

Abstract: Cell adhesion molecules (CAMs) are pivotal in establishing and maintaining synaptic connectivity. Emerging evidence indicates that some secreted factors within the synaptic cleft,

including C1q-like proteins (C1qls), play a crucial role in bridging pre- and post-synapses by connecting the bilateral CAMs. However, the mechanisms of those secreted factors in synapse assembly remain incomplete. Here, we explored C1ql-mediated synaptic connectivity, focusing on the assembly of C1ql1 and its post-synaptic receptor brain-specific angiogenesis inhibitor 3 (BAI3). Our biochemical, structural, and computational analyses reveal that the trimeric globular C1q (gC1q) domain of C1ql1 undergoes a calcium-modulated domain-swapping event to form a hexamer. Cryo-EM study manifests the stabilizing role of calcium ions on the C1ql1-gC1q hexamer in complex with the extended CUB domain of BAI3. Using the gC1q hexamer, full-length C1ql1 further assembles into linear clusters, creating a scaffold that effectively accumulates BAI3 receptors on the plasma membrane. Our cellular and in vivo studies consolidate the essential role of the gC1q-mediated dynamic assembly of C1ql1 in receptor accumulation and synapse maintenance. Collectively, our findings provide a plausible mechanism of secreted factor-mediated synaptic connectivity, driven by the calcium-modulated assembly of C1qls and their interactions with CAMs.

Disclosures: Y. Han: None. B. Zhang: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.04/A41

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: MSCA Postdoctoral Fellowship

Title: The role of synapse polarity on the formation of inhibitory connections

Authors: *A. MASET, V. MENNE, G. NEVES, J. BURRONE;
Ctr. for Developmental Neurobio., King's Col. London, London, United Kingdom

Abstract: A central question in neuroscience is how neurons in the brain wire up during development. In the cortex, inhibitory (GABAergic) interneurons regulate the activity of pyramidal excitatory (glutamatergic) neurons, which is vital for circuit function throughout life. During development, various interneurons establish synapses with specific subcellular regions of pyramidal neurons. This occurs sequentially, with the first synaptic contacts forming at the somato-dendritic compartment, and lately at the axon initial segment (AIS). Although GABA serves as the main inhibitory neurotransmitter in adults, during early development, GABAergic synaptic transmission can exert a depolarising effect with widespread trophic influences (Ben-Ari, 2002). GABA signalling prompts outward chloride currents, leading to depolarisation, as immature neurons maintain high chloride levels via NKCC1 transporter activity. The downregulation of NKCC1, along with upregulation of KCC2, leads to chloride extrusion and a shift from high to low chloride levels, converting GABA from depolarising to hyperpolarising. This process is essential for brain development and influences lifelong function. We propose that

depolarising GABA stabilises GABAergic synapses during their formation. To test this hypothesis, we characterised the subcellular chloride landscape and GABAergic contacts by pharmacologically blocking NKCC1, reducing intracellular chloride. We used the ratiometric chloride sensor LSSmClpHensor (Sulis-Sato et al., 2017) to track intracellular chloride levels during development and Fibronectin intrabodies (FingRs) attached to Gephyrin (Gross et al., 2013) to assess inhibitory synapse distribution on pyramidal cells. Pyramidal neurons show relatively elevated chloride levels after the second postnatal week, presenting a gradient of intracellular chloride concentration ($[Cl^-]_i$) that varies from the dendrites to the axon initial segment (AIS). Reducing $[Cl^-]_i$ during synapse formation in dendrites or AIS decreased GABAergic synapse density, indicating that high chloride levels are vital for synapse formation. Conversely, reducing $[Cl^-]_i$ after dendritic synapse establishment increased synaptic density. Our data bear out that the GABA polarity switch at different subcellular sites follows a unique and precise temporal sequence. High chloride is initially necessary for inhibitory synapse formation but later contributes to essential processes like synapse stabilisation and pruning.

Disclosures: A. Maset: None. V. Menne: None. G. Neves: None. J. Burrone: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.05/A42

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01 DC007695

Title: A cell polarity program defines somatic innervation territory and dendrite location during neural circuit formation

Authors: P. S. HOLCOMB¹, M. MOREHEAD³, M. H. ELLISMAN², *G. A. SPIROU⁴;

¹Sensory Neurosci. Res. Ctr., Sch. of Med., Morgantown, WV; ²Dept Neurosci, Sch. of Med., La Jolla, CA; ³Istovisio, Inc, Morgantown, WV; ⁴Univ. of South Florida, Tampa, FL

Abstract: Cell polarity programs are integral to nervous system development. They establish intracellularly ordered arrangements of organelles to guide cell migration and specify the initial extension of dendrites and axon, and position cell types that reside in laminar arrangements. Using serial block-face scanning electron microscopy across neonatal ages (P2-P9) in mice, 3D reconstruction of neurons and organelles reveals that principal neurons (PN) of the MNTB, which are somatically innervated by the large calyx of Held (CH) nerve terminal, maintain an eccentric nucleus position that defines a somatic polarity vector. Since this age range encompasses growth of the CH and completion of its circuit topography, we hypothesized that cell polarity would generalize to other aspects of cell and circuit development. Cell polarity extends to dendrite emergence primarily from locations on the somatic surface away from the nucleus called the cytoplasmic pole (CP). The mean angle of all dendrites by age was: P2, 72.5 ±

27°; P3, $67.3 \pm 38^\circ$; P4, $73 \pm 43^\circ$; P6, $70.5 \pm 44^\circ$; P9, $77 \pm 23^\circ$ (Values 0-90° from the polarity vector define the CP). Dendrites are transient, reducing in number over just a few days from 5.2 ± 1.2 at P2 to 2.5 ± 0.52 at P6. Dendrites likely function as capture nets for incoming axons, because most afferent axons that form the CH track along dendrites to their somatic innervation locus (P3, 15/16; P4, 12/16). Plots of innervated somatic surface in rings defined along the polarity vector revealed that relative to random placement of a large input, the CH grows on the CP ($p < 0.0001$), concordant with the CP location of most dendrites. We next investigated whether all PNs had similar orientations of cell polarity vectors. Vector strength analysis revealed the orientation of PNs to be random across the cell group (all values < 0.5 : P2, 0.43; P3, 0.23; P4, 0.23; P6, 0.24). These events define for the first time an expanded cell polarity program that extends retrogradely to the dominant synaptic input, applies to a non-laminar cell group, and supports a dendrite capture hypothesis that underlies polarized innervation.

Disclosures: **P.S. Holcomb:** None. **M. Morehead:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership interest, syGlass, Inc.. **M.H. Ellisman:** None. **G.A. Spirou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership interest, syGlass, Inc..

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.06/A43

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH EY019498
NIH EY019498
NIH EY019498
NIH EY028625
Society of Hellman Fellows
McKnight foundation
Glaucoma Research Foundation

Title: Activity-dependent changes in the synaptic proteome of retinal direction-selective circuit.

Authors: ***R. SOMAIYA**¹, M. A. PO¹, E. LIANG², J. OSES-PRIETO⁴, M.-M. FU¹, K. SHEKHAR³, M. B. FELLER¹;

¹Univ. of California, Berkeley, Berkeley, CA; ²Univ. of California, Berkeley, Tucson, AZ;

³Chem. and Biomolecular Engin., Univ. of California, Berkeley, Berkeley, CA; ⁴Univ. of California, San Francisco, San Francisco, CA

Abstract: The mechanism of synapse specificity - the ability of presynaptic neurons to select a subset of available postsynaptic partners - is an outstanding question in nervous system

development. We study this phenomenon in the direction selective circuit of the retina.

Direction-selective ganglion cells (DSGCs) encode the direction of the visual motion. Different subtypes of DSGCs respond most strongly to an object moving in one of four cardinal directions (dorsal, ventral, nasal, or temporal) and weakly to motion in the opposite or null direction. This computation is dependent on their precise wiring with the processes of an inhibitory interneuron called starburst amacrine cell (SAC).

The establishment of direction-selective circuits coincides with the occurrence of retinal waves, a form of spontaneous activity resulting in periodic depolarizations of immature RGCs, including DSGCs. We found that that disrupting retinal waves leads to a dramatic reduction in the directional tuning of DSGC subtypes preferring horizontal motion while maintaining the directional tuning of those preferring vertical motion. Strikingly, the transcriptome of DSGCs in these mice have no major activity-dependent changes, suggesting that activity does not influence the cell-intrinsic genetic programs to instruct synaptic specificity in the retinal direction-selective circuit.

In this study, we test the hypothesis that activity influences SAC-DSGC synaptic specificity required for horizontal direction selectivity through post-transcriptional mechanisms. Using ChAT^{Cre};SyntdT^{fl/fl} mice, where SAC presynapses are fluorescently-labeled, we isolated SAC synaptosomes, which includes pre- and postsynapse, via sucrose gradient centrifugation and magnetic bead sorting. These mice were also crossed with β 2KO mice, which lack the β 2 subunit of the nicotinic acetylcholine receptor, resulting in the disruption of retinal waves, to generate an activity-perturbed group. We then performed quantitative mass spectrometry on isolated SAC synaptosomes to assess how activity perturbation alters the synaptic proteome. This approach allows us to identify molecular changes specifically at SAC synapses in the presence or absence of retinal waves. Here, we will present the first high-throughput, activity-dependent synaptic proteome map of a well-defined retinal microcircuit, offering insights into how spontaneous activity regulates synaptic composition and partner specificity.

Disclosures: R. Somaiya: None. M.A. Po: None. E. Liang: None. M. Fu: None. K. Shekhar: None. M.B. Feller: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.07/A44

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: This work was supported by funding received from Indian Council of Medical Research (ICMR), Anusandhan National Research Foundation (ANRF) and Pratiksha Trust (India)
National Nanofabrication Facility and Micro Nano Characterization Facility at the Indian Institute of Science is acknowledged for support with device fabrication

Dr Deepak Nair is acknowledged for help with super resolution synaptic imaging

Title: Investigating neurite growth and guidance on scaffolds with micro/nano topographies

Authors: *V. GAUTAM;

Ctr. for NanoScience and Engin., Indian Inst. of Sci., Bangalore, India

Abstract: The extracellular matrix (ECM) in the brain plays a vital role in its development and function. However, the precise mechanisms by which neurons interact with the physicochemical cues in the ECM remain unclear. Advances in nanofabrication techniques now allow for specific nano/micro-scale patterns to be designed as physical cues on substrates for neuronal culture. When combined with advanced imaging and electrophysiology techniques, these scaffolds offer a platform to study neuron-ECM interactions. We have previously shown that hippocampal neurons cultured on isotopically arranged nanopillar structures (200-600nm diameter, 2 μm gap) align their projections along the nanopillar topography¹. In this study, we show that neurite guidance can also be observed on micropillars with width and gap of 2-3 μm . Micropillars were fabricated by replica molding of Polydimethylsiloxane (PDMS) from a silicon stamp with varying diameters and gaps of 2 μm , 3 μm , 4 μm , 5 μm and 10 μm and arranged vertically over a 0.25 mm² (500 μm x 500 μm) area on a PDMS substrate. Primary hippocampal neurons from postnatal rat pups (P0-P2) were cultured on the scaffolds. At DIV 7, neuronal growth was assessed using confocal and electron microscopy. Compared to flat controls, neurons on micropillars exhibited greater neurite length per cell, increased branching, and larger nuclear size. Notably, neurites predominantly grew at 0° and 90° angles on pillars with 2 or 3 μm gap, regardless of pillar width. In order to explore the mechanisms underlying neurite guidance on micropillars, we incorporated super resolution microscopy to image the expression of pre- (Bassoon) and post- (Shank) synaptic markers in neurites on the micropillars. Our results indicate enhanced synaptic connectivity on micropillar substrates. Complementary whole-cell patch-clamp recordings revealed altered current amplitudes and kinetics (rise and decay times) in neurons cultured on micropillars. This presentation will draw inferences on how neurons respond to physical cues in their extracellular environment and discuss how this information can be used to modulate or design functional in vitro neuronal networks.¹ Gautam, V. et al. Engineering Highly Interconnected Neuronal Networks on Nanowire Scaffolds. 17(6) 3369-3375 (Nano Lett, 2017)

Disclosures: V. Gautam: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.08/A45

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Department of Defense ONR#000141010198
NIH 1R15AG045820-01A1
NIH R21MH135232-01A1

Title: Separate functional domains of hippocampal NMDA receptors in juvenile mice influence spatial navigation

Authors: *A. BOAKYE-AGYEI¹, D. GONZALEZ², T. C. DUMAS³;
¹George Mason Univ. Interdisciplinary Neurosci. Phd Program, Fairfax, VA; ²George Mason Univ. Interdisciplinary Neurosci. Phd Program, Arlington, VA; ³Psychology, George Mason Univ., Fairfax, VA

Abstract: Patterns of activity-dependent alterations in the efficacy of excitatory synapses in the hippocampus serve as engrams for spatial context and are reliant on activation of N-methyl-D-aspartate receptors (NMDARs). In rodents, spatial learning and memory matures around three weeks of age, coinciding with altered NMDAR subunit composition. As synapses mature, NMDARs containing GluN2B subunits are replaced by NMDARs containing GluN2A subunits. This shift alters the threshold for induction of synaptic plasticity and is thought to permit rapid and detailed contextual encoding. NMDARs permit calcium to enter postsynaptic neurons if agonist binding occurs concurrent with postsynaptic depolarization (ionotropic signaling). NMDARs can also produce postsynaptic signals without ion influx (metabotropic signaling). Metabotropic signaling is believed to be mediated via the intracellular carboxy terminal domains (CTDs) of GluN2 subunits. Thus, swapping CTDs between GluN2A and GluN2B subunits permits investigation of the separate contributions of GluN2A- and GluN2B-type ionotropic and metabotropic contributions to engram formation. We created transgenic mice expressing chimeric GluN2A-B^{ctd} or GluN2B-A^{ctd} subunits and tested them as juveniles in the Morris water maze to study how NMDAR ionotropic and metabotropic signaling impact the emergence of spatial learning and memory. Fifteen training trials were performed on the same day in blocks of three trials each. Probe trials were delivered immediately after training and 24 hours following training. At P17-18, escape latency and path length significantly decreased across training blocks in all genotypes, indicating learning. However, there were no quadrant biases within groups, and no genotype effect on directness to goal during the immediate or 24-hour probe suggesting incomplete or latent memory formation at this stage. We continue to analyze data from mice trained at P22-23, after the GluN2B-GluN2A shift. A better understanding of NMDAR signaling in the juvenile period would clarify the mechanisms behind the changing cognitive ability observed during development. Together, they elucidate the etiology and contribute towards treatment of neurodevelopmental disorders, particularly those where NMDAR dysfunction is implicated.

Disclosures: A. Boakye-Agyei: None. D. Gonzalez: None. T.C. Dumas: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.10/A46

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH P20GM148302

Title: Developmental vulnerability to brain injury is driven by complement-dependent synaptic pruning: A targetable window in early life

Authors: *D. BARAN¹, A. LAVIN², O. ALBAYRAM³;

¹Pathology and Lab. Med., Med. Univ. of South Carolina (MUSC), Charleston, SC; ²Dept Neurosci., Med. Univ. of South Carolina (MU Neurosci. Inst. - Grad., Charleston, SC;

³Pathology and Lab. Med., Med. Univ. of South Carolina, Charleston, SC

Abstract: The early postnatal brain undergoes rapid synaptic remodeling, rendering it uniquely vulnerable to injury-induced disruptions in developmental pruning. Here, we identify a critical, targetable window during which repetitive mild traumatic brain injury (rmTBI) induces maladaptive synapse elimination via complement component 3 (C3)-dependent microglial pruning. Using a closed-head rmTBI model in male C57BL/6J mice at postnatal days (PD) 14 and 60, we discovered that only early postnatal injury leads to persistent cognitive deficits, implicating age-dependent complement dynamics. Behavioral assays revealed that PD14 rmTBI—but not PD60—causes long-term risk-taking behavior and spatial memory deficits in adolescence, as measured by the elevated plus maze, T-maze, and Barnes maze. Two weeks post-injury, the PD14 cortex showed robust C3 deposition at synapses, elevated microgliosis, and marked dendritic degeneration. Whole-cell patch-clamp recordings from the injured cortex showed reduced excitatory postsynaptic current amplitudes and action potential firing, indicating a long-term loss of functional glutamatergic synapses. Ultrastructural analysis confirmed reduced synapse number and increased microglial phagocytosis of synaptic material. To mechanistically link aberrant pruning to behavioral outcomes, we administered CR2-Crry, a C3 activation inhibitor, beginning one hour after injury. CR2-Crry treatment rescued dendritic density, preserved synapse number, and prevented long-term behavioral deficits. Immunohistochemical analysis revealed that CR2-Crry significantly reduced C3/MAP2/Iba1 and LAMP1 colocalization at microglial-neuronal interfaces, indicating reduced engulfment of C3-opsonized synapses. Electrophysiological recovery in excitatory synaptic transmission further corroborated the protective effects of C3 inhibition. Together, these findings reveal that the developing brain is selectively vulnerable to injury-induced complement activation and highlight C3-mediated pruning as a tractable target to prevent long-term cognitive consequences of pediatric brain trauma. Our results establish a developmental framework for understanding how timing of injury dictates trajectory, and demonstrate that early intervention can recalibrate microglial responses to preserve synaptic architecture and function. **Keywords:** complement system, C3, microglia, synaptic pruning, pediatric brain injury, neurodevelopment, CR2-Crry, electrophysiology, dendritic degeneration.

Disclosures: D. Baran: None. A. Lavin: None. O. Albayram: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.11/A47

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: W. M. Keck Foundation Junior Faculty Award

Title: The role of gap junctions in developmental neural activity

Authors: *J. M. MILLER, J. REICHL;
Neurobio., UCLA, Los Angeles, CA

Abstract: The developing brain becomes electrically active before it can receive external sensory stimuli. This intrinsic activity facilitates circuit maturation throughout the developing central nervous system (CNS) in vertebrates. Uncovering the cellular and molecular mechanisms which drive and coordinate this process remains an important challenge in the field of developmental neuroscience. The invertebrate counterpart of developmental activity was recently discovered in the fruit fly, *Drosophila melanogaster*. Patterned, stimulus-independent, neural activity (PSINA, 'see-nah') occurs during the two days before the adult animal emerges from metamorphosis, and comprises globally coordinated minutes-long cycles of active and silent phases which engage the entire CNS. More recently, we identified the neurons that are critical to establishing these stereotyped activity cycles: Loss-of-function of the SIFamide (SIFa) neuropeptide gene or electrical silencing of the four peptidergic neurons which express SIFa (aka SIFa neurons) severely disrupt the periodic activity cycles of PSINA. Gap junctions are known to be essential for developmental activity in mammals, but their roles in PSINA have not been explored. There are eight gap junction genes, or innexins, in the fly. Focusing initially on the most well-characterized innexin, Shaking-B (ShakB), I discovered that it is necessary in SIFa neurons for wildtype PSINA. Specifically, ShakB knockdown in SIFa neurons disrupts of the periodic temporal organization of PSINA, suggesting that ShakB is necessary for the wildtype physiology and function of these critical neuropeptidergic neurons. This finding not only opens the door to mechanistic studies of SIFa neuron activity during development, it also strongly motivates a much-needed push to investigate the role of all eight gap junction genes in regulating developmental activity in the fly. Thus, **the focus of this project is to establish the roles of innexins in PSINA**. I will characterize how the *ShakB* gene and ShakB gap junctions participate in PSINA. In addition, I will assess the function of the other seven innexins in PSINA. I expect these studies to yield critical mechanistic insights that will extend our understanding of how PSINA is driven and patterned. This deeper understanding will in turn support and refine our efforts to investigate the circuit and behavioral level consequences of disrupting developmental activity.

Disclosures: J.M. Miller: None. J. Reichl: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.12/A48

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH R01 NS045193
NIH R01 MH115750
NIH U19 NS104648
CV Starr Fellowship (Starr Foundation)

Title: Psilocybin recovery of tactile discrimination after early postnatal sensory deprivation

Authors: *E. SEFIK, V. S. ZHANG, C. JUNG, L. A. LYNCH, S. S.-H. WANG;
Princeton Neurosci. Institute, Princeton Univ., Princeton, NJ

Abstract: Sensitive periods are temporally restricted phases of development during which experience-dependent plasticity can shape neural circuits and exert enduring effects on brain function. We tested the hypothesis that psychedelics, which alter dendritic spine dynamics (e.g. Shao et al., 2021; Sefik et al., 2024) and which can restore youthful levels of social reward learning (Nardou et al., 2023; however, see Lu et al., 2025), can facilitate sensory recovery following early-life deprivation. Here, we report a preliminary test of psilocybin's ability to rescue adult tactile discrimination following early-life sensory deprivation. In male and female C57BL/6J mice, we trimmed all whiskers at P0, P5, P10, P15, or P20. After whiskers regrew to normal adult length (~2.5 cm, median age = P67), we gave mice a single dose of psilocybin (2 mg/kg, i.p.) or saline. 48 hours later, beyond the acute phase of psilocybin's action, we assessed whisker-dependent texture discrimination using the textured Novel Object Recognition Test (tNORT, N = 98 mice), which leverages the ethologically conserved exploratory drive of mice to investigate novel over familiar tactile stimuli at above-chance levels. Untrimmed mice performed the task successfully (median novelty discrimination index = 61%, one-sample t-test vs. 50% chance, $p = 0.02$). Consistent with previous work (Lu et al., 2025), psilocybin administration in unperturbed mice did not produce persistent effects on novel object recognition (median index = 62%, two-sample t-test vs. saline, $p = 0.17$). Among trimmed groups, psilocybin-treated mice trimmed at P15, an age coinciding with a period of experience-dependent strengthening of L4-L2/3 and L2/3-L2/3 synapses in barrel cortex, exhibited the greatest recovery of tactile discrimination in adulthood (median index = 66% for P15-trimmed psilocybin vs. 53% for P15-trimmed saline), in contrast to no age-dependent recovery in saline-treated mice. Linear regression revealed a trend-level positive effect of whisker trimming age on performance in the psilocybin group ($\beta = 0.90$, $p = 0.07$), but not in the saline group ($\beta = -0.11$, $p = 0.80$). Segmented regression further identified an inflection point at P15 selectively in the psilocybin group, with a positive slope before and a flattening or negative slope after the breakpoint, consistent with the hypothesis that its plasticity-promoting effects are gated by developmental timing. Ongoing work is increasing sample size and incorporating exploratory behavior metrics to strengthen statistical inference and behavioral resolution. Future experiments will incorporate dendritic spine imaging to probe the link with synaptic plasticity.

Disclosures: E. Sefik: None. V.S. Zhang: None. C. Jung: None. L.A. Lynch: None. S.S. Wang: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.13/A49

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Title: Glutamatergic IL-1R1 Drives Early Life Stress-Induced Social Dysfunction via Hippocampal Circuit Reorganization

Authors: *M. C. MONET^{1,2}, M. I. SMIRNOVA³, D. NEMETH⁴, N. QUAN⁵;

¹Max Planck Florida Inst. for Neurosci., Jupiter, FL; ²Intl. Max Planck Res. Sch. for Synapses and Circuits, Jupiter, FL, United States, Jupiter, FL; ³Biomed. Sci., Intl. Max Planck Res. Sch. for Synapses and Circuits, Jupiter, FL; ⁴Col. of Med., ⁵Florida Atlantic Univ., Jupiter, FL

Abstract: Early life stress (ELS) heightens the risk of neurodevelopmental disorders characterized by impaired social interaction. The interleukin-1 receptor type 1 (IL-1R1), a key mediator of inflammatory signaling in the brain, is upregulated by stress and has been implicated in long-term behavioral changes. However, the specific role of glutamatergic IL-1R1 in ELS-induced social deficits remains unclear. Here, we used a maternal separation (MS) model of ELS in combination with conditional IL-1R1 transgenic mice to determine the temporal and cellular contributions of glutamatergic IL-1R1 to stress-induced behavioral and molecular outcomes. We observed a developmentally dynamic pattern of glutamatergic IL-1R1 expression in the dentate gyrus (DG), with pronounced localization to the outer granule cell layers between postnatal days 7 and 14. In parallel, we mapped IL-1R1 expression across the developing brain and are preparing an EBRAIN atlas capturing region- and time-specific IL-1R1 profiles. Our data reveal a progressively increasing IL-1R1 expression in the DG and a transient wave of IL-1R1 expression in the ventral posteromedial (VPM) thalamic nucleus—active between postnatal day 2 and 14—which projects to the somatosensory barrel cortex. MS exposure led to elevated glutamatergic IL-1R1 and Δ FosB expression in DG neurons, accompanied by enduring social interaction deficits in adulthood. Notably, pharmacological blockade of IL-1R1 during the postnatal period prevented the emergence of MS-induced social abnormalities. To test whether glutamatergic IL-1R1 is necessary and/or sufficient for these outcomes, we employed cell type-specific IL-1R1 knockout and rescue strategies. Loss of glutamatergic IL-1R1 protected against MS-induced social and anxiety-like behaviors, while selective re-expression of IL-1R1 in DG granule neurons reinstated the behavioral phenotype. These findings identify a critical developmental window during which ELS modulates social behavior via glutamatergic IL-1R1 signaling, and support targeting IL-1R1 in excitatory circuits as a strategy to prevent long-term effects of early life adversity.

Disclosures: M.C. Monet: None. M.I. Smirnova: None. D. Nemeth: None. N. Quan: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.14/A50

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Title: The Spatiotemporal Profile of Synaptotagmin 2 in Sensory Neurons during Synaptogenesis

Authors: *S. SABBAGH, S. BEST, Y. WANG;

Program in Neuroscience, Dept. of Biomed. Sciences, Col. of Med., Florida State Univ., Tallahassee, FL

Abstract: Synaptotagmin 1 and 2 (Syt1 and Syt2) are Ca^{2+} sensors on synaptic vesicles, essential for action potential-triggered neurotransmitter release from presynaptic terminals. Following axon-dendrite contact formation, Syt1 and Syt2, along with other presynaptic proteins, are rapidly upregulated in newly formed terminals to initiate neurotransmission. Emerging evidence suggests that synapse position and dendritic configuration influence signal integration and processing maturation. However, the spatiotemporal trajectory of Syt2-containing functional synapses during early development remains unclear. In this study, we examined the maturation pattern of excitatory synapses on dendrites, using Syt2 as a marker for functional synapses. Bipolar neurons in the chicken nucleus laminaris (NL) provide an excellent model. Individual NL neurons receive segregated inputs on their dorsal and ventral dendritic domains from the ipsilateral and contralateral nucleus magnocellularis (NM), respectively, acting as coincidence detector by encoding temporal features between the two inputs in the microsecond range. We performed quantitative analyses of Syt2 immunocytochemistry at four developmental milestones: E9 (initial NM-NL contact), E11 (onset of NM-NL synaptogenesis), E15 (NL dendrite and synapse reorganization), and E19 (mature-like circuit connection). We found that Syt2 immunoreactivity was not distributed evenly between the dendritic domains. First, the ventral domain exhibited high overall Syt2 density at all ages, suggesting a higher release probability in response to contralateral action potentials during development and maturation. Second, Syt2 density in the ventral domain showed a gradient during the early stages at E9 and E11, with higher levels proximally and a gradual decline distally. As the circuit matures, this gradient disappeared at E15 and E19. Conversely, Syt2 intensity remained uniform in the dorsal domain at all ages. These observations indicate that the formation of functional synapses is progressed differentially in different dendritic domains of the same neurons. Finally, we found that knocking down FMRP, an RNA-binding protein, significantly delayed in Syt2 upregulation and synapse functionalization onset. Together, our findings suggest that the regulated spatial variations in Syt2 may play a role in shaping transient, position-specific aspects of synapse maturation and functionalization.

Disclosures: S. Sabbagh: None. S. Best: None. Y. Wang: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.15/A51

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIMH R21MH127486
NINDS T32 TRAINING GRANT
THE SCHMITT PROGRAM FOR INTEGRATIVE NEUROSCIENCE

Title: Maternal Separation Alters Synaptic Remodeling in the Paralamina Nucleus of the Amygdala

Authors: *D. P. KING¹, A. K. MAJEWSKA², J. L. CAMERON³, J. L. FUDGE⁴;
¹Neurosci., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; ²Neurosci., Univ. of Rochester, Rochester, NY; ³Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; ⁴Dept of Neurosci. and Psychiatry, Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: The paralamina nucleus (PL) of the amygdala contains a unique population of immature, post-mitotic glutamatergic neurons that mature between infancy and adolescence. Microglia are thought to support maturation through synaptic pruning during this critical developmental window. We previously showed that maternal separation induces a hyper-ramified microglial phenotype in PL (King et al., eNeuro, 2025). Here, we tested whether this altered morphology corresponds to changes in microglial engulfment of synaptic elements. We analyzed postmortem brain tissue from infant and adolescent macaques that were either maternally reared (MR) or separated from their mothers at 1 week (1-WS) or 1 month (1-MS) of age. Using immunocytochemistry, we quadruple-labeled microglia (IBA1), the lysosomal marker CD68 (macrosialin), and the synaptic markers Syn1 (presynaptic) and PSD95 (postsynaptic). Confocal microscopy and Imaris analyses were used to first quantify Syn1+ boutons, PSD95+ puncta, and putative excitatory synapses (Syn1/PSD95 colocalization). Then, we analyzed the volume of engulfed synaptic elements by phagocytically active microglia. In infants but not adolescents, maternal separation resulted in significant reductions in Syn1+ boutons ($p = 0.0006$), PSD95+ puncta ($p = 0.0005$), and putative synapses (Syn1/PSD95 colocalization, $p = 0.0028$). Syn1+ boutons ($p < 0.0001$), PSD95+ puncta ($p < 0.0001$) and putative synaptic contacts ($p < 0.0001$) all decreased with age across all groups, consistent with age-related 'pruning'. Maternal separation resulted in greater microglial volume in the infants ($p = 0.0006$) compared to control. Overall, microglial volume increased with age ($p < 0.0001$). Maternal separation also increased the phagocytic index value (CD68/IBA1 colocalization) in the separated infants, and in 1-MS adolescent PL ($p = 0.0004$). Both 1-WS and 1-MS infants had increased engulfment of Syn1+ boutons ($p = 0.0488$) and PSD95 puncta ($p = 0.0045$) compared to control. Between infancy and adolescence, across all groups there was also increased engulfment of PSD95 puncta and SYN1 boutons except for the 1MS group ($p < 0.0001$). The age-related increase in the engulfment of putative synaptic contacts was observed only in the MR and 1-WS groups ($p <$

0.0001). Maternal separation increased the engulfment of putative synapses only in the 1-MS infant group ($p = 0.1165$). We conclude that maternal separation accelerates microglial mediated synaptic pruning. We speculate that overly aggressive engulfment during infancy may deprive immature neurons in the PL of essential trophic input, disrupting their maturation and long-term integration into amygdala circuitry.

Disclosures: D.P. King: None. A.K. Majewska: None. J.L. Cameron: None. J.L. Fudge: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.16/A52

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01MH129732
Brenton R. Lutz Award

Title: A pipeline for Abberior STED super-resolution imaging and Imaris analysis of nanoscale synapse organization in mouse cortical brain slices

Authors: *E. KRUZICH;

Cell. Imaging Core, Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Understanding the fine structure of synaptic connections is essential for elucidating the functional architecture of cortical circuits, particularly in brain regions implicated in neuropsychiatric disorders. Here, we present a streamlined experimental and analytic pipeline for high-resolution visualization of apical dendritic spines in layer 1 of the mouse prefrontal cortex. This protocol integrates brain slice preparation, immunostaining, and imaging using an Abberior Facility Line STED super-resolution microscope at the Cellular Imaging Core of Boston University Medical Campus (BUMC). Data processing and quantitative morphometric analysis are conducted using the Imaris software platform. The pipeline is optimized to preserve sub-diffraction spine morphology and enables robust extraction of nanoscale structural features. This approach supports detailed investigations of experience-dependent plasticity and structural abnormalities in dendritic spines, facilitating studies of synaptic pathophysiology in models of psychiatric disease.

Disclosures: E. Kruzich: None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.17/A53

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Georgetown University Provost Grant

Title: 3-d mapping and regional density determinations of epha receptors and ephrina ligand binding patterns during synaptogenesis in the postnatal mouse brain

Authors: *L. F. KROMER¹, I. K. LORENZEN², B. EASTWOOD², J. R. GLASER², N. J. O'CONNOR²;

¹Georgetown Univ. Med. Ctr., Washington, DC; ²MBF Biosci., Williston, VT

Abstract: EphA tyrosine kinase receptors and their ephrinA binding partners are cell surface signaling molecules that are critically important for regulating the topographic organization of the brain connectome. Due to the complexity of Eph and ephrin expression and their importance for brain synaptic circuit development, we have developed computer assisted whole brain imaging software that provides a more efficient tool for generating 3D maps of these molecules within the entire CNS. This program contains a new workflow software using the NeuroInfo platform (MBF Bioscience) that aligns and reconstructs images of mouse brain sections labeled with histochemical techniques into whole-brain 3D images. The images are subsequently registered to the DevCCF developing mouse brain atlas (Kronman et al., 2023) a 3D, multimodal, undistorted brain atlas aligned with the Allen Institute's Common Coordinate Framework (CCFv3) reference template and annotations (Wang et al., 2020). Following registration to the DevCCF, staining intensity is calculated for each brain region and normalized per brain for standardized comparison across receptor and ligand distributions in different cohorts. To demonstrate the feasibility of this imaging program, we evaluated the hippocampus and adjacent dentate gyrus. Serial slide sets from postnatal day 6 mice were stained for EphA4 and EphA7 proteins using a standard BDA immunohistochemical staining procedure. Additional specimens were processed to identify the distribution and density of ephrinA binding patterns as described previously (Tai, et al., 2013). 3D rendering of images demonstrated the feasibility of this program to map small subregional differences in the localization and density of EphA4 vs EphA7 receptors along with subtle subregion and laminar specific variations in ephrinA2, A3, A4, and ephrinA5 binding. Our data identified unique regional density differences for EphA receptors and ephrinA ligand binding. EphA4 exhibits low expression within the CA1-CA3 and dentate granule cell layers, whereas EphA7 has high expression in CA1 and CA3 only. EphA4 is more highly expressed in stratum oriens and stratum lucidum of CA3 and exhibits a distinct and dense lamina specific staining in stratum radiatum of CA1 - CA3. EphA7 is weakly expressed in CA2 and adjacent CA3, but more diffusely in stratum radiatum of CA1. Both receptors were localized to the inner zone of the dentate molecular layer. Similar unique regional and layer specific ephrinA binding is observed and can be cross mapped to the EphA receptor patterns. This new 3D mapping system should greatly enhance data acquisition and analysis for studies on brain circuit formation.

Disclosures: L.F. Kromer: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Research Support. I.K. Lorenzen: A. Employment/Salary (full or part-

time): MBF Bioscience. **B. Eastwood:** A. Employment/Salary (full or part-time): MBF Bioscience. **J.R. Glaser:** A. Employment/Salary (full or part-time): MBF Bioscience. **N.J. O'Connor:** A. Employment/Salary (full or part-time): MBF Bioscience.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.18/A54

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant GR530272
NIH Grant T32NS115705

Title: Sez6L2 regulates synaptic connectivity by inhibiting complement-mediated pruning during neurodevelopment

Authors: ***J. GRANATO**¹, J. RANDOLPH², J. W. HAMMOND²;
¹Dept. of Neurosci., ²Dept. of Neurol., Univ. of Rochester, Rochester, NY

Abstract: Sez6L2 is a neuron-specific protein that our lab has identified as a novel inhibitor of complement deposition *in vitro*. The deposition of complement protein C3b on synaptic surfaces is an important mechanism of synaptic pruning during neurodevelopment. Additionally, Sez6L2 has been recognized as a genetic risk factor associated with neurodevelopmental disorders such as autism spectrum disorder (ASD). Therefore, this study aims to determine how Sez6L2 impacts complement activity and synaptic pruning during development. To investigate this mechanism, we examined how different domains of Sez6L2 contribute to its inhibitory activity. We show that splice variants lacking a BACE1-mediated cleavage site have stronger inhibition of complement deposition relative to variants that contain this cleavage site. Additionally, we found that the front region of the Sez6L2 protein, which includes alternating CCP and CUB domains, is necessary for its proper function. Notably, we also show that Sez6L2 specifically binds to complement-initiating protein C1q, as well as multiple other complement components and synaptic proteins. In a microglial phagocytosis assay, synaptic material that lacks Sez6L2 is preferentially engulfed by microglia compared to wildtype (WT) synaptosomes, suggesting that the loss of Sez6L2 may promote synaptic removal by disinhibiting complement deposition. Indeed, this preference is lost when C3/CR3 signaling is inhibited. Consistent with these *in vitro* assays, we also show that juvenile mice with a genetic knockout (KO) of Sez6L2 exhibit elevated cortical levels of complement protein C3 by western blot. Finally, we show that postnatal day 10 (P10) Sez6L2 KO mice have decreased synaptic density in the lateral geniculate nucleus (LGN). Overall, our data have implications for the important role of Sez6L2 in modulating complement activity during key neurodevelopmental periods, leading to aberrant complement-mediated synaptic pruning and abnormal brain development.

Disclosures: **J. Granato:** None. **J. Randolph:** None. **J.W. Hammond:** None.

Poster

PSTR003: Synapse and Circuit Formation, Maturation, and Remodeling

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR003.19/A55

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: R01-MH126017

Title: Snx27-mediated recycling of nl4x

Authors: *A. C. QUINTERO-GONZALEZ, O. BENNER, S. CHANDA;
Biochem. & Mol. Biol., Colorado State Univ., Fort Collins, CO

Abstract: Neuroligins (NLGNs) are a group of postsynaptic cell-adhesion molecules that interact with presynaptic Neurexins (NRXNs) to modulate synaptic properties. Disruptions in NLGN trafficking due to pathogenic mutations, can result in mental disorders such as Autism Spectrum Disorders and Schizophrenia. Neurons express multiple NLGN isoforms, e.g., NLGN1-3, that are well conserved across different species. However, the function of a human-specific NLGN4X isoform and its mechanisms of synaptic trafficking remain unclear to date. Moreover, it is unknown how individual domains and/or residue(s) contribute to NLGN4X synaptic trafficking and function. Here, we investigated which recycling machinery associates with NLGN4X to modulate its recycling between endosomes and the cell surface. We found that NLGN4X interacts with the retromer complex through binding with sorting nexin 27 (SNX27), a cargo adaptor protein that is highly enriched in human brains. This interaction arises already during early neurodevelopmental stages. SNX27 binds to NLGN4X through its class I PDZ domain, and when NLGN4X PDZ domain is deleted, this interaction is abolished. Together, we show that the cell-surface population of NLGN4X is potentially regulated via its interactions with the retromer recycling machinery.

Disclosures: A.C. Quintero-Gonzalez: None. O. Benner: None. S. Chanda: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.01/A56

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

Support: Secihti-Mexico grants 255087 and CF-2023-I-935
Secihti-ECOS-Nord 3135689

Title: Circadian Modulation of glial neurotransmitter transporter in Retina Müller cells

Authors: *T. I. SUBAIR¹, B. O. OYETAYO², L. C. HERNANDEZ³, A. ORTEGA⁴;
¹Toxicology, Ctr. de Investigación y Estudios Avanzados, Mexico City, Mexico; ²Toxicology, Ctr. for Res. and Advanced Studies of the Natl. Polytechnic Inst., Ciudad de Mexico, CDMX, Mexico; ³Toxicología, ⁴Toxicology, Cinvestav-IPN, Mexico City, Mexico

Abstract: The visual signal transmission of the retina is primarily characterized by the stimulation of glutamate, the main excitatory neurotransmitter in the central nervous system. Glutamate transactions are carried out through two subtypes of receptors, namely ionotropic and metabotropic glutamate receptors. However, overstimulation of these receptors is known to cause neuronal death, a process known as excitotoxicity. A family of plasma membrane, sodium-dependent glutamate transporters, mostly expressed in glial cells, is critically involved in the uptake and recycling process, limiting receptor activation and thus preventing an excitotoxic event. These transporters are called excitatory amino acid transporters (EAATs) and are mostly expressed in glial cells. Within the retina, the vast majority of glutamate uptake occurs in Müller glial cells (MGC). In this study, we focused on the involvement of circadian rhythmicity in MGC glutamate transporter activity, taking into consideration the well-established light-dependent differential glutamate release in the retina. Synchronized cells (50% SFB) were used in this study, and uptake activity was measured through [³H]-D-Aspartate transport. The results show a differential glutamate uptake activity across 24 hours, indicating a plausible role of clock genes in the uptake. This data supports the notion an exquisite regulation of Müller glia glutamate transport and further strengthens the role of radial glia cells in retina physiology.

Disclosures: T.I. Subair: None. B.O. Oyetayo: None. L.C. Hernandez: None. A. Ortega: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.02/A57

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

Support: CONAHCYT 935751

Title: Satellite glial cells synthesize and release GABA, which activates extrasynaptic GABA receptors that modulate the excitability of sensory neurons

Authors: *N. JIMÉNEZ BARRIOS¹, F. J. PAZ¹, R. GONZALEZ-RAMIREZ^{3,4}, R. FELIX², J. RAYA TAFOYA¹, G. B. FLORAN¹, R. DELGADO-LEZAMA¹;
¹Physiology, Biophysics and Neurosciences, ²Cell Biol., CINVESTAV, Mexico City, Mexico; ³Dept. of Mol. Biol. and Histocompatibility, Gen. Hosp. Dr. Manuel Gea González, Mexico City, Mexico; ⁴Ctr. for Res. on Aging (CIE), Mexico City, Mexico

Abstract: Sensory neurons (SN), whose cell bodies are located in the dorsal root ganglia (DRG), are responsible for transmitting sensory information and are surrounded by satellite glial cells (SGC). SN does not receive axosomatic synapses but expresses extrasynaptic GABA_A receptors (GABA_AR) α_5 GABA_A and α_6 GABA_A, although the source of the GABA that activates them is unknown. SGC uptake [³H]GABA and release it independently of Ca²⁺ extracellular concentration, possibly through the Bestrofin1 channel (Best1). Nevertheless, it has been suggested that GABA is synthesized and released in SN. That is why there is a controversy about which of the two cells synthesizes and releases the GABA that activates extrasynaptic GABA_AR in DRG. Conventionally, it has been accepted that GABA is synthesized from glutamate by glutamate decarboxylase 65 and 67 (GAD65 and GAD67). However, alternative synthesis pathways use ornithine and convert it into putrescine to produce GABA by monoamine oxidase B (MAOB) or diamine oxidase (DAO). This study investigated the expression and functional role of enzymes involved in the GABA synthesis pathways, the mechanisms underlying GABA release, and their impact on SN excitability. To this end, we employed PCR, Western blotting, and immunofluorescence techniques to identify the presence and localization of mRNA and proteins associated with GABA synthesis, uptake, degradation, and release in rat DRG. In addition, we utilized neurochemical approaches to assess GABA synthesis and release, and electrophysiological recordings to evaluate the functional activation of extrasynaptic GABA_AR. Our findings indicate that while mRNA for GAD65 and GAD67 was detected in the DRG, the corresponding proteins were not. MAOB and DAO were expressed in SGC; however, only inhibition of MAOB led to a reduction in GABA accumulation in primary SGC cultures. GABA, GABA transporter 3, and GABA transaminase were localized exclusively in SGC, whereas Best1 was expressed in both neurons and SGC. [³H]GABA release was found to be independent of extracellular Ca²⁺ but dependent on intracellular Ca²⁺ levels, and it was significantly reduced upon inhibition of Best1. Inhibition of MAOB and Best1, but not DAO or GAD, increased excitability of primary afferent fibers. These findings suggest that GABA can be synthesized via the ornithine-MAOB pathway and released through Best1 channels from SGC, activating extrasynaptic GABA_AR and reducing SN excitability.

Disclosures: N. Jiménez Barrios: None. F.J. Paz: None. R. Gonzalez-Ramirez: None. R. Felix: None. J. Raya tafoya: None. G.B. Floran: None. R. Delgado-Lezama: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.03/A58

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

Support: NIH 1R01NS127819-01

Title: iGABASnFR reveals the persistence of GABA in the extracellular space following synaptic activity

Authors: ***R. L. GARIEPY**¹, C. G. DULLA², M. ARMBRUSTER²;

¹Tufts Univ. Grad. Program In Neurosci., Boston, MA; ²Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Following synaptic activity, the excitatory neurotransmitter glutamate is rapidly cleared from the extracellular space, as shown using glutamate transporter currents, iGluSnFR imaging, and NMDA currents. However, much less is understood about the clearance of gamma-aminobutyric (GABA), the primary inhibitory neurotransmitter. GABAergic inhibition is critical for maintaining homeostasis and regulating neuronal activity. It consists of phasic, synaptic inhibition and tonic inhibition driven by distinct GABA receptors located in different cellular compartments. Therefore, understanding the spatiotemporal characteristics of GABA in the extracellular space after release has important implications on downstream inhibition. Utilizing iGABASnFR, a fluorescent sensor that increases its fluorescence upon binding to GABA, we developed the first optical assay of GABA clearance from the extracellular space following synaptic activity. Our results show that GABA persists in the extracellular space greater than 500 ms after bursts of activity. Using iGABASnFR decay time ($T_{80}-T_{20}$), we also find that GABA remains in the extracellular space more than twice as long following bursts of 10 stimuli, as compared to following a single stimulation. We next examined the role of GABA transporters (GATs) on iGABASnFR decay time. Following the pharmacological inhibition of GATs, GABA clearance is significantly slowed, consistent with their role in shaping GABAergic inhibition. Interestingly, GAT function peaks 0.5-1 second after the end of the stimulus suggesting a significant role for passive diffusion in addition to active transport. Results also show that the time of GABA clearance is dependent on the amount of focal GABA released; as the peak of GABA increases, the persistence of GABA in the extracellular space also increases. In addition to low magnification iGABASnFR imaging, modeling and high magnification confocal imaging shows that GATs function primarily outside of GABA release sites. Together, these results reveal a striking contrast in neurotransmitter dynamics: GABA clearance is slow and prolonged, compared to the tightly controlled clearance of glutamate by astrocytes. This highlights distinct mechanisms of GABA accumulation and clearance separate from phasic IPSC dynamics.

Disclosures: **R.L. Gariepy:** A. Employment/Salary (full or part-time): Tufts University Graduate School of Biomedical Sciences. **C.G. Dulla:** A. Employment/Salary (full or part-time): Tufts University School of Medicine. **M. Armbruster:** A. Employment/Salary (full or part-time): Tufts University School of Medicine.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.04/A59

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

Support: NINDS R25NS09098502
McDonnell Center for Systems Neuroscience Small Grants Program

GF0012518
NIDA T32DA007261

Title: Electroconvulsive shock activates hippocampal GABAergic interneurons in mice

Authors: *N. D. L. KABBAJ¹, J. BILBILY⁴, O. J. KRENTZMAN², C.-C. KUO³, C. R. VAZQUEZ⁵, J. G. MCCALL⁶;

¹Dept. of Anesthesiology, Washington Univ. in St. Louis, ²Anesthesiology, Ctr. for Clin. Pharmacol., ³Dept. of Anesthesiol., Washington Univ. in St. Louis, St. Louis, MO; ⁴Dept. of Psychiatry, Washington Univ. in St. Louis Sch. of Med., St Louis, MO; ⁵Anesthesiology, Ctr. for Clin. Pharmacol., Washington Univ. In St. Louis, Saint Louis, MO; ⁶Anesthesiology, Ctr. for Clin. Pharmacol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Electroconvulsive therapy (ECT) has been used for more than 80 years for treatment-resistant psychiatric disorders, including depression, bipolar disorder, schizophrenia, and catatonia. ECT requires multiple sessions and produces a generalized seizure that is critical for its therapeutic effects. Despite ECT's remarkable efficacy, its mechanism of action remains unknown. The GABA hypothesis proposes that increased GABAergic neuronal activity drives ECT's therapeutic effects. To investigate this, we administered eight sessions of Sham (control) or electroconvulsive shock (ECS) treatment to C57 mice (n=8). We found that ECS in mice increases the proportion of parvalbumin (PV) expressing GABAergic cells labeled with c-Fos (an immediate early gene that serves as a marker for neuronal activity) in the mouse hippocampus (6.09% Sham vs. 25.26% ECS). Since ECT requires a brain-wide seizure over multiple sessions, we also wanted to investigate its effects across the brain, both acutely and chronically. We compared mice given one session of ECS to a longer-term, clinically relevant setting (seven sessions). Working with four groups of C57 mice (n=24), we administered either one or seven sessions of Sham or ECS treatment before perfusing mice and extracting the intact brain. In partnership with LifeCanvas, whole brains were cleared and stained globally using immunohistochemistry for GABAergic interneurons such as PV and somatostatin (SST), and for c-Fos. We constructed 3D maps of the above markers' brain-wide expression to monitor evolving changes between sham and ECS across 1 and 7 sessions. Preliminary results of analysis suggest cortical increases in c-Fos globally and specifically in PV and SST cells. In sum, we have found that ECS in mice increases c-Fos activity specifically in PV-expressing cells in the hippocampus, and preliminary results suggest this pattern is replicated widely in the cortex. Further analysis will reveal more about the specific circuits ECS may act on. Strengthening our understanding of the mechanism of action of ECT will be crucial in developing more targeted treatments for treatment-resistant psychiatric disorders.

Disclosures: N.D.L. Kabbaj: None. O.J. Krentzman: None. C. Kuo: None. C.R. Vazquez: None. J.G. McCall: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.05/A60

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

Support: Erasmus Mundus ENC program
NSFC32100761
ANR-12-JSV4-0005-01 VGLUT-IQ ;
ANR-10-LABX-43 BRAIN
ANR-10-IDEX-03-02 PEPS SV-PIT
CRC 1286 "Quantitative Synaptology" project A11

Title: A minor impact of VGLUT1 expression level on quantal size revealed through the characterization of VGLUT1^{mEos2} knock-down new mouse model

Authors: *X. ZHANG¹, N. LIPSTEIN², E. HERZOG³;
¹Sun Yat-sen Univ., Guangzhou, China; ²Dept. of Mol. Neurobio., Goettingen, Germany;
³Interdisciplinary Inst. For Neurosci., Bordeaux, France

Abstract: Synaptic vesicles (SVs) are small organelles secreting neurotransmitters at synapses. By fusing a photoactivated fluorescent protein to VGLUT1, we generated a VGLUT1^{mEos2} knock-in mouse. VGLUT1^{mEos2} knock-in mice are viable and healthy, but exhibit a severe reduction in VGLUT1 expression levels. Using VGLUT1^{mEos2} expressing neurons, we established paradigms to trace individual SV mobility at the single-molecule level or via massive photoconversion. Hippocampal neurons with significantly diminished VGLUT1 expression maintain unaltered miniature glutamate release characteristics in terms of quantal size and frequency. We demonstrate that VGLUT1 expression level are not correlated in a linear fashion with the vesicular glutamate content. In conclusion, the VGLUT1^{mEos2} mouse line serves as a powerful tool for exploring SV mobility properties and elucidating the contributions of VGLUT1 to excitatory neurotransmission and cognitive processes.

Disclosures: X. Zhang: None. N. Lipstein: None. E. Herzog: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.06/A61

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

Support: Research Training Program Scholarship

Title: Serotonin influences sensory signalling in cortical pyramidal neurons

Authors: *Y. WANG^{1,2}, T. QIAN^{1,2}, M. ROSIER^{1,2}, L. M. PALMER^{1,2};
¹The Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia; ²The Univ. of Melbourne, Melbourne, Australia

Abstract: Neuromodulation is a fundamental process which influences how the brain processes information. Although serotonin (5-HT) is recognised for its role in modulating higher-order brain function, its impact on sensory processing and learning is largely unknown. In particular, little is known about the role of the two primary receptor subtypes of 5-HT, the inhibitory 5-HT_{1A} and the excitatory 5-HT_{2A} receptors, on sensory encoding in the cortex. This was addressed here using whole-cell patch clamp electrophysiological recordings from layer 2/3 pyramidal neurons within the primary somatosensory cortex (S1) during tactile stimulation in anaesthetised and awake behaving mice. We found that sensory signalling was bidirectionally altered by 5-HT_{1A} and 5-HT_{2A} receptor activation, with an increase and decrease in tactile-evoked voltage responses respectively. Following learning of a sensory-association task, the behaviourally-evoked sensory voltage response was decreased during pharmacological block of 5-HT_{2A} receptors. Together, these results illustrate that 5-HT modulates sensory signalling in cortical pyramidal neurons in vivo, contributing to a deeper understanding of the role of the serotonergic system in cortical function.

Disclosures: Y. Wang: None. T. Qian: None. M. Rosier: None. L.M. Palmer: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.07/A62

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

Support: US, NIH Grant R01NS112176
US, NIH Grant R01NS129549
US, NIH Grant R42NS125895
Republic of Korea, KHIDI Grant HI19C075300
Republic of Korea, Korea University Grant (the startup research fund for new faculty of the College of Informatics)
Republic of Korea, MoHW RS-2024 00413115
Republic of Korea, MFDS 25212MFDS004

Title: Effects of oxycodone on tonic levels and phasic release of serotonin in the rat nucleus accumbens core

Authors: *Y. KWAK^{1,3}, J. M. ROJAS CABRERA³, S. VETTLESON-TRUTZA³, K. SCHEITLER³, U. KARANOVIC³, C. D. BLAHA³, Y. OH³, H. SHIN³, D. JANG^{2,3}, K. H. LEE³;
²Biomed. Engin., ¹Hanyang Univ., Seoul, Korea, Republic of; ³Neural Engin. and Precision Surgery Lab. - Dept. of Neurologic Surgery, Mayo Clin., Rochester, MN

Abstract: Oxycodone is a potent opioid widely prescribed for pain management. However, its misuse has significantly contributed to the opioid overdose epidemic. While dopamine has been extensively studied in the context of opioid use disorder, serotonin—also critically involved in

mood regulation, impulsivity, and addiction—has received less attention. Conventional neurochemical techniques such as microdialysis lack the temporal resolution required to capture rapid serotonin fluctuations. In contrast, electrochemical methods including fast-scan cyclic voltammetry and N-shaped multiple cyclic square wave voltammetry, when combined with carbon fiber microelectrodes, enable real-time detection of phasic release and tonic concentrations of extracellular serotonin. We employed fast-scan cyclic voltammetry and N-shaped multiple cyclic square wave voltammetry to investigate the acute effects of intravenous oxycodone (2.5 mg/kg) on serotonergic neurotransmission in urethane-anesthetized male Sprague-Dawley rats. Recording electrodes were implanted in the nucleus accumbens core. Phasic serotonin release was evoked by medial forebrain bundle stimulation (300 μ A, 60 Hz, 2 ms, 120 biphasic pulses). Serotonin kinetics—production concentration and maximum reuptake rate—were analyzed using the Michaelis-Menten model. Tonic serotonin levels were measured without stimulation. Oxycodone increased tonic serotonin levels by 26.23% from baseline and maintained this elevation throughout the recording session. Phasic serotonin release rose sharply by 24% immediately after administration but gradually declined below baseline. Serotonin production and reuptake rates also initially increased, followed by a subsequent decrease below baseline. Oxycodone acutely alters serotonergic transmission in the nucleus accumbens core, distinctly modulating phasic and tonic serotonin dynamics. These findings highlight the utility of in vivo electrochemical techniques for capturing rapid neurochemical changes associated with opioid administration.

Disclosures: Y. Kwak: None. J.M. Rojas Cabrera: None. S. Vetteson-Trutza: None. K. Scheitler: None. U. karanovic: None. C.D. Blaha: None. Y. Oh: None. H. Shin: None. D. Jang: None. K.H. Lee: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.08/B1

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

Support: Grant ASAP-020370

Title: Neuromodulation of striatal serotonin transmission in health and a mouse model of early parkinsonism

Authors: *Q. QIAO^{1,3,4}, H. M. COLLINS^{2,3,4}, P. J. MAGILL^{2,3,4}, S. J. CRAGG^{1,3,4};
¹Physiology, Anatomy and Genet., ²MRC Brain Network Dynamics Unit, Univ. of Oxford, Oxford, United Kingdom; ³Aligning Sci. Across Parkinson's (ASAP) Collaborative Res. Network, Chevy Chase, MD; ⁴Oxford Parkinson's Dis. Ctr., Oxford, United Kingdom

Abstract: The striatum receives dense dopaminergic (DA) input from the midbrain and sparser serotonergic (5-HT) input from the raphe nuclei. Striatal 5-HT has been implicated as opposing

striatal DA function and also indirectly regulating DA release. However, how 5-HT release is controlled has been unclear until the recent development of a genetically encoded 5-HT sensor (GRAB_{5-HT3.0}; Deng et al., 2024), enabling direct detection of 5-HT dynamics. We investigated how striatal 5-HT release reported by striatal expression of GRAB_{5-HT} is regulated by DA, acetylcholine (ACh), and GABA and their receptors, in acute *ex vivo* brain slices from healthy and parkinsonian mice.

We firstly characterised evoked GRAB_{5-HT} signals and validated their specificity for 5-HT in dorsolateral striatum (DLS) and nucleus accumbens core (NAcC). Evoked signals were greater and decayed faster in NAcC than DLS, consistent with greater 5-HT axon innervation density in NAcC. For comparison, GRAB_{5-HT} signals evoked in the substantia nigra pars reticulata (SNr), a region with dense 5-HT innervation, were an order of magnitude larger, consistent with detection of 5-HT not DA. Furthermore, striatal GRAB_{5-HT} signals were prolonged by SSRI citalopram, while unilateral 6-OHDA injections into the SNc to lesion striatal DA innervation reduced DA release detected by fast-scan cyclic voltammetry, but did not alter 5-HT signals. Together, these characteristics are consistent with detection of 5-HT rather than DA in the striatum. We next explored how evoked striatal 5-HT release was modulated by local neurotransmitter systems. 5-HT release was facilitated by D₁R agonist SKF81297 and inhibited by D₂R agonist quinpirole, effects abolished by D₁R or D₂R antagonists. Nicotinic AChR (nAChR) antagonist DHβE or muscarinic (mAChR) agonist oxotremorine-M also modified 5-HT signals, with mAChR effects requiring intact nAChRs, indicative of upstream regulation by mAChRs of ACh release acting at nAChRs. GABA_A&B_R antagonists together enhanced 5-HT release, suggesting tonic GABAergic inhibition of 5-HT signalling. Studies underway in a mouse model of early Parkinson's disease (PD) overexpressing human alpha-synuclein have indicated attenuated D₂R-mediated inhibition of 5-HT release in DLS, suggesting disease-associated disruption of DA-5-HT interaction. In summary, our findings show robust detection of striatal 5-HT and reveal that striatal 5-HT release is regulated by diverse dopaminergic, cholinergic, and GABAergic circuits. This integrative control is compromised in a PD model, providing insight into broader network dysfunction that may underlie neuromodulator imbalance in PD.

Disclosures: Q. Qiao: None. H.M. Collins: None. P.J. Magill: None. S.J. Cragg: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.09/B2

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

Support: GVSU Office of Undergraduate Research and Scholarship Supplies Grant
P. Douglas Kindschi Undergraduate Research Fellowship in the Sciences
PHS R01AA030577

Title: Effect of melatonin on striatal cholinergic interneuron-mediated dopamine transmission

Authors: *J. WEBB¹, M. KOLANOWSKI², E. RAMSSON³, J. T. YORGASON⁴;

¹Wake Forest Univ., Winston-Salem, NC; ³Biomed. Sci., ²Grand Valley State Univ., Allendale, MI; ⁴Cell. Biol. and Physiol., Brigham Young Univ., Provo, UT

Abstract: Melatonin is a major circadian hormone whose primary physiological function is to convey information concerning the daily cycle of light and darkness. This circadian cycle affects the neurotransmission of many neurotransmitters, including dopamine, which peaks during the dark phase and is lowest during the light phase in mice. Additionally, dopamine release can be influenced by acetylcholine release onto dopaminergic terminals from tonically active cholinergic interneurons. The purpose of this study is to better understand how melatonin affects the firing dynamics of cholinergic interneurons in the striatum and subsequently changes dopamine transmission. Fast-scan cyclic voltammetry in mouse brain slices showed that melatonin exposure causes a sex-dependent response in dopamine release that relies on cholinergic interneuron activation. Application of 4-AP, a voltage-gated potassium channel antagonist, caused an increase in dopamine release in both males and females, but when melatonin was subsequently added, dopamine release further increased in males but decreased in females, possibly due to inactivation of nicotinic acetylcholine receptors or depolarization block. Treatment with melatonin followed by 4-AP caused an increase in dopamine release in females, while males showed no direct change to melatonin but a decrease in dopamine when 4-AP was added. Additionally, in both males and females, striatal cholinergic interneurons treated with melatonin showed a decrease in firing frequency as measured with cell-attached patch-clamp electrophysiology. However, melatonin did not directly affect dopamine neuron firing frequency. These results suggest cholinergic interneurons play a role in regulating melatonin-dependent changes to dopamine transmission in a sex-dependent manner.

Disclosures: J. Webb: None. M. Kolanowski: None. E. Ramsson: None. J.T. Yorgason: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.10/B3

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

Title: Cholinergic interneurons exert prolonged control over dopaminergic axonal excitability

Authors: *V. GHOSH¹, P. F. KRAMER²;

²MCDB, ¹Univ. of Michigan, Ann Arbor, MI

Abstract: Dopamine (DA) release is critical for reward learning and movement, and dysregulated DA release can lead to neurological disorders like substance use disorder and Parkinson's disease. DA release is controlled by both somatic and axonal modulation. One key source of axonal modulation comes from acetylcholine-releasing striatal cholinergic interneurons

(CINs) in the dorsal striatum and nucleus accumbens. CINs modulate dopaminergic (DAergic) axonal excitability through nicotinic and muscarinic acetylcholine receptors (nAChRs and mAChRs). Recent *in vitro* studies show a direct relationship between CIN activation and DA release, such that CINs evoke phasic depolarizations in DAergic axons which can elicit action potentials and DA release. However, *in vivo* studies find a more complex relationship, suggesting features of CIN-mediated control over dopaminergic axonal excitability that are currently not understood. In order to examine how CINs control dopaminergic axonal excitability, we use a new technique that allows for direct electrophysiological recordings of dopaminergic axons. . In axons, a key determinant of excitability is the resting membrane potential, as that sets the overall channel availability and membrane biophysics. We examined the DAergic axon resting membrane potential (RMP) in the striatum and nucleus accumbens using perforated-patch recordings and found a change in the RMP on antagonizing nAChRs. To examine the functional output of this RMP modulation, we examined direct recordings from spontaneously spiking axons and found significant changes in the waveform upon altering the RMP. Remarkably, we saw a change in peak amplitude as well as in the “half-width” of the spike indicating possible underlying changes in spike-mediated calcium entry. Thus, we provide evidence that CIN mediated synaptic transmission on DA axons tightly controls its excitability through nAChRs, and dysfunction in this process could have significant effects on DA axon spiking.

Disclosures: V. Ghosh: None. P.F. Kramer: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.11/B4

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

Support: NIH/NIDA Grant R01DA056547
SUNY Research Seed Grant Award (RFP#23-01-RSG)
NIH/NIDDK Grant R01DK128030

Title: Decoding A2 noradrenergic innervation of the bed nucleus of the stria terminalis in reward and aversion through neurochemical sensing and chemogenetic techniques

Authors: *R. V. BHIMANI¹, C. E. BASS², E. G. MIETLICKI-BAASE³, J. PARK⁴;
¹Biotechnical and Clin. Lab. Sci., Univ. At Buffalo, Buffalo, NY; ²955 Main Street, Univ. At Buffalo SUNY, Buffalo, NY; ³Exercise and Nutr. Sci., Univ. of Buffalo, Buffalo, NY;
⁴university at buffalo-SUNY, buffalo, NY

Abstract: The A2 noradrenergic (NE) neurons of the nucleus of the solitary tract (NST) are critical for the regulation of autonomic processes and affective states. Importantly, A2-NE neurons densely innervate (~9% of all brain NE) the ventral bed nucleus of the stria terminalis (vBNST), a key structure implicated in stress, anxiety, and addiction. However, little is known

regarding the role of A2-NE signaling in the vBNST in reward/aversion due to their relatively small size and proximity to other catecholamine rich brain regions. Using cell-type specific chemogenetic manipulations in wild-type, male and female rats, we selectively expressed designer receptors exclusively activated by designer drugs (DREADDs) on A2 noradrenergic neurons and activated or inhibited A2 neurons to investigate their impact on NE transmission in the vBNST and behavior. Chemogenetic activation of A2 neurons increased NE release in the BNST and led to robust behavioral changes. In both the light/dark box and open field tests, activation resulted in reduced locomotor activity and decreased time spent in anxiogenic zones, suggesting enhanced anxiety-like behavior. In contrast, chemogenetic inhibition of A2 neurons attenuated NE signaling and produced anxiolytic-like effects. Given the BNST's role in drug-seeking and stress-induced relapse, these findings suggest that A2 neurons modulate circuits underlying both affective behavior and addiction-related processes. Thus, the A2-BNST pathway may serve as a novel therapeutic target for anxiety-related and drug use disorders.

Disclosures: **R.V. Bhimani:** None. **C.E. Bass:** None. **E.G. Mietlicki-Baase:** None. **J. Park:** None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.12/B5

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

Support: KAKENHI Grants-in-Aid for Scientific Research (A) (18H04081)
KAKENHI Grants-in-Aid for Scientific Research (A) (21H04858)
KAKENHI Grants-in-Aid for Scientific Research (A) (24H00670)
KAKENHI Grants-in-Aid for Scientific Research on Innovative Areas (16H06405)
Japan Science and Technology Agency (JST)-Mirai Program (JPMJMI19D5)
Grant-in-Aid for Japan Society for the Promotion of Science Fellowships (20J20887)

Title: Slow Running Triggers Dopaminergic and Noradrenergic Stimulation in the Dorsal Hippocampus.

Authors: ***T. HIRAGA**^{1,2}, T. HATA^{1,2}, S. SOYA^{3,4}, R. SHIMODA¹, K. TAKAHASHI¹, M. SOYA¹, K. INOUE⁶, J. P. JOHANSEN⁷, M. OKAMOTO^{1,2}, H. SOYA^{1,5};

¹Inst. of Hlth. and Sport Sci., ²Advanced Res. Initiative for Human High Performance (ARIHHP), ³Intl. Inst. for Integrative Sleep Med. (WPI-IIIS), ⁴Inst. of Med., ⁵Ctr. for Cybernics Res., Univ. of Tsukuba, Tsukuba, Japan; ⁶Ctr. for Educ. in Liberal Arts and Sci., Hlth. Sci. Univ. of Hokkaido, Ishikari, Japan; ⁷Ctr. for Brain Sci., RIKEN Ctr. for Brain Sci., Wako, Japan

Abstract: Physical exercise benefits the brain, particularly the learning and memory center—the dorsal hippocampus (dHPC)—and holds promise as a therapeutic strategy for addressing age-related cognitive decline. While moderate-to-vigorous-intensity exercise is commonly recommended for general health, our translational research in both animals and humans has focused on light-intensity exercise (light exercise) such as slow running, which can be performed safely and with minimal stress by most individuals. We have previously shown that even light exercise can activate hippocampal neurons and enhance memory performance. Although the underlying circuit mechanisms remain unclear, previous findings indicating exercise-induced activation of the monoaminergic system—which is essential for modulating hippocampal plasticity and memory—suggest that monoaminergic stimulation may contribute to the hippocampal benefits of light exercise. To test this hypothesis, we employed a rat treadmill running model based on a physiological indicator common to both humans and animals: the lactate threshold. In this model, we assessed the neuronal activation in the dHPC and brainstem monoaminergic nuclei using c-Fos-based immunohistochemistry and monitored extracellular monoamine concentrations in the dHPC using *in vivo* microdialysis combined with the high-performance liquid chromatography. We found that even slow running, corresponding to light exercise, increased neuronal activity in dHPC sub-regions (DG, CA1, and CA3), and elevated extracellular levels of dopamine (DA) and noradrenaline (NA), but not serotonin (5-HT). Furthermore, tyrosine hydroxylase-positive (TH⁺) neurons in the locus coeruleus (LC) and the ventral tegmental area (VTA) were also activated by slow running, whereas 5-HT-producing neurons in the raphe nuclei were not. Further correlation analyses revealed that activation of TH⁺ neurons in both the LC and the VTA was positively associated with dHPC activation. In conclusion, our findings suggest that slow running stimulates dHPC neurons in association with LC-noradrenergic and VTA-dopaminergic pathways. These results shed light on the circuit mechanisms underlying light-exercise-induced hippocampal activation and provide a potential neural basis for its memory-enhancing effects.

Disclosures: T. Hiraga: None. T. Hata: None. S. Soya: None. R. Shimoda: None. K. Takahashi: None. M. Soya: None. K. Inoue: None. J.P. Johansen: None. M. Okamoto: None. H. Soya: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.13/B6

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

Support: KAKENHI Grants-in-Aid for Scientific Research (A): 18H04081
KAKENHI Grants-in-Aid for Scientific Research (A): 21H04858
KAKENHI Grants-in-Aid for Scientific Research (A): 24H00670
KAKENHI Grants-in-Aid for Scientific Research on Innovative Areas:
Next Generation Exercise Program for Developing Motivation, Body and
Mind Performance: 16H06405

Japan Science and Technology Agency (JST)-Mirai Program:
JPMJMI19D5
Grant-in-Aid for Japan Society for the Promotion of Science Fellowships:
21J20478
Grant-in-Aid for Japan Society for the Promotion of Science Fellowships:
22KJ0362

Title: Emerging neuronal pathway underlying thiamine-derivative-induced active physical behavior: Dopaminergic coeruleo-prefrontal cortical pathway

Authors: *T. HATA^{1,2}, T. HIRAGA^{3,2}, M. OKAMOTO^{3,2}, H. SOYA^{3,4};

¹Grad. Sch. of Comprehensive Human Sci., Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; ²Div. of Sport Neuroscience, Kokoro Division, Advanced Res. Initiative for Human High Perform, ³Inst. of Hlth. and Sport Sci., ⁴Ctr. for Cybernics Res., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Physical activity is essential for maintaining physical and mental health. However, many people worldwide fail to meet the physical activity levels recommended by the World Health Organization. Therefore, developing nutraceutical strategies to enhance motivation for an active lifestyle and elucidating their underlying neurobiological mechanisms remain critical needs. We previously reported that thiamine tetrahydrofurfuryl disulfide (TTFD), a thiamine (vitamin B1) derivative, promotes voluntary physical activity in rats by increasing dopamine (DA) release in the medial prefrontal cortex (mPFC) (Saiki *et al.*, 2018), and induces arousal (Hata *et al.*, 2025), suggesting its potential as a nutraceutical intervention. Although DA in the mPFC is primarily derived from the ventral tegmental area (VTA), recent attention has focused on the co-release of DA and noradrenaline from the locus coeruleus (LC), raising the possibility that both pathways may be involved. To investigate this, we employed in vivo microdialysis, immunohistochemistry, and pharmacological approaches using 11-week-old male Wistar rats. First, we simultaneously measured physical activity and extracellular monoamine levels in the mPFC following intraperitoneal injection of TTFD (50 mg/kg; Vehicle: Saline). Double-immunostaining for c-Fos and tyrosine hydroxylase (TH) revealed that TTFD selectively increased DA in the mPFC and activated TH-positive neurons in both the VTA (VTATH) and LC (LCTH) (n = 9/group). Next, retrograde tracing was used to assess the activation of mPFC-projecting VTATH or LCTH neurons after TTFD injection and revealed that only LCTH neurons projecting to the mPFC (LCTH→mPFC) were activated following TTFD treatment (n = 7/group). Finally, inhibition of LC neuronal activity using the α 2-adrenergic receptor agonist clonidine attenuated both the TTFD-induced increase in DA levels in the mPFC and the enhancement of voluntary physical activity (n = 7/group). Here we found that the LCTH→mPFC pathway plays a crucial role in mediating TTFD-induced enhancement of physical activity. Collectively, these findings together with our previous results suggest that TTFD may promote physical activity by activating LC-derived dopaminergic neurons projecting to the mPFC, proposing an innovative neuronal substrate underlying a promising nutraceutical strategy.

Disclosures: T. Hata: None. T. Hiraga: None. M. Okamoto: None. H. Soya: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Tsukuba.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.14/B7

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

Support: JSPS KAKENHI Grant Numbers JP19H03221 (YH), JP22H02716 (YH), JP22K18939 (YT), and JP22KJ1098 (YD)
AMED Grant numbers JP19dm0207082 (YH), JP21wm0525015 (YH)
JST, PRESTO Grant Number JPMJPR16F7 (YH)
NIH - NINDS - R35 NS127232 (FP)
NIH - NIGMS – R35 GM137921 (TLL)

Title: Most axonal mitochondria in neurons of the mammalian central nervous system lack mitochondrial DNA and consume ATP

Authors: *Y. HIRABAYASHI¹, T. LEWIS, Jr.², Y. DU¹, E. ZAMPONI³, D. VIRGA⁵, Y. SUGIURA⁶, I. TESTA⁷, F. POLLEUX⁴;

¹Univ. of Tokyo, Tokyo, Japan; ²Aging and Metabolism, Oklahoma Med. Res. Fndn., Oklahoma City, OK; ³Neurosci., ⁴Dept Neurosci., Columbia Univ., New York, NY; ⁵Columbia Univ. Program In Neurobio. And Behavior, New York, NY; ⁶Kyoto Univ., Kyoto, Japan; ⁷applied physics, SciLifeLab, KTH, Stockholm, Sweden

Abstract: Mitochondria-dependent ATP synthesis is classically thought to support energy-consuming neuronal functions, including presynaptic neurotransmitter release. However, only 50% of presynaptic boutons along the axons of cortical pyramidal neurons (CPNs) contain mitochondria, making the contribution of presynaptic mitochondria to ATP supply in the axon unclear. Axonal mitochondria are also significantly smaller (~1 micron) than their somatodendritic counterparts, raising questions about their oxidative phosphorylation (OXPHOS) capacity. To address this, we assessed the presence of mitochondrial DNA (mtDNA) in individual axonal mitochondria in developing and mature mouse CPNs both in vitro and in vivo. Using multiple independent approaches—including immunofluorescence detection of mtDNA and associated proteins, as well as quantitative PCR from single axonal mitochondria isolated using fluorescence-based scanning ion conductance microscopy, we found that mtDNA is undetectable in ~80% of axonal mitochondria. Live imaging revealed that axonal mitochondria do not generate significant ATP, unlike dendritic mitochondria. Instead, complex V (ATP synthase) predominantly functions in reverse, consuming ATP to maintain mitochondrial membrane potential. These findings challenge the traditional view that axonal mitochondria serve as major ATP producers and suggest they play other critical roles, such as presynaptic calcium buffering and amino acid synthesis, which are required for proper neurotransmitter release.

Disclosures: Y. Hirabayashi: None. T. Lewis: None. Y. Du: None. E. Zamponi: None. D. Virga: None. Y. sugiura: None. I. Testa: None. F. Polleux: None.

Poster

PSTR004: Neurotransmitters

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR004.15/B8

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

Support: Indian Council of Medical Research

Title: Early pregnancy levels of Amino Acid Neurotransmitters: Can it predict development of Gestational Diabetes or depressive symptoms and serve as potential markers for Perinatal Mood Disorders?

Authors: *P. GHOSH¹, M. DEEPA², A. RANJIT MOHAN³, U. RAM⁴, V. MOHAN², P. SARAVANAN⁵, K. GOKULAKRISHNAN⁶, B. SRIKUMAR⁷;

¹Natl. Inst. of Mental Hlth. and Neurosciences, Bengaluru, India; ²Dept. of Diabetology, Madras Diabetes Res. Fndn. (MDRF), Chennai, India; ³Madras Diabetes Res. Fndn. (MDRF), Chennai, India; ⁴Seethapathy Clin. & Hosp., Chennai, India; ⁵Univ. of Warwick, Nuneaton, UK, United Kingdom; ⁷Neurophysiol., ⁶Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India

Abstract: Globally, it is estimated that 10-15% of women suffer from depression during pregnancy and the postpartum period, while 8-10% gets affected from anxiety disorders. Neurotransmitters play a key role in regulating mood, behaviour, and emotional responses, however the interconnection of classical amino acid neurotransmitter systems with maternal behaviour during pregnancy, at parturition and lactation remains largely unknown. Given the bidirectional relationship between depression and gestational diabetes mellitus (GDM), this study aimed to profile amino acid neurotransmitters in a nested cohort of women selected from the STRatification of Risk of Diabetes in Early Pregnancy (STRiDE) study. Participants included women with normal fasting glucose levels and no depressive symptoms during early pregnancy (<16 weeks). During the OGTT visit at 24-28 weeks, a 75 g OGTT and PHQ-9 assessment were performed. Women were categorized into four groups (n=16, each): Normal glucose tolerance without development of depressive symptoms (NGT), NGT subjects who developed depressive symptoms (NGT+DS), Pregnant women who developed GDM but not depressive symptoms (GDM), and subjects who developed both GDM and depressive symptoms (GDM+DS). The plasma levels of amino acid neurotransmitters such as Aspartate, Glutamate, Serine, Glutamine, Glycine, Taurine, GABA from early pregnancy were measured using reversed-phase high-performance liquid chromatography (RP-HPLC) coupled with fluorescence detection. In the GDM+DS group, Aspartate levels were significantly higher when compared to NGT or GDM groups. Glutamate levels were higher only in the GDM+DS group when compared with NGT. There was a marginal elevation in Glutamine and Serine levels in the GDM group, which accentuated in the GDM+DS group. In both GDM and GDM+DS groups, there was a significantly higher levels of Taurine and GABA, while Taurine levels were marginally higher in the NGT+DS group, while GABA was not affected. Glycine was largely unaffected by either

GDM or DS. Thus, Serine, Glutamine, Taurine and GABA levels were higher only in subjects who developed GDM and Aspartate was higher only in those who developed depressive symptoms, while glutamate was increased only with subjects who developed both GDM and DS. The observed alterations in neurotransmitter-related amino acids associated with maternal depression and gestational diabetes mellitus suggest underlying pathophysiological mechanisms and highlight the potential of peripheral amino acid profiling as a biomarker strategy for detecting mood and metabolic disorders during pregnancy.

Disclosures: P. Ghosh: None. M. Deepa: None. A. Ranjit Mohan: None. U. Ram: None. V. Mohan: None. P. Saravanan: None. K. Gokulakrishnan: None. B. Srikumar: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.01/B9

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

Title: Co-expression of Receptor-Associated Proteins Enables Drug Discovery Targeting $\alpha 5$ -Containing Nicotinic Acetylcholine Receptors

Authors: *S. GU¹, D. BREDET²;

²Neuroscience, Discovery, ¹Rapport Therapeut., San Diego, CA

Abstract: Nicotine addiction remains a significant public health challenge and a leading cause of lung cancer, with its addictive properties mediated by nicotinic acetylcholine receptors (nAChRs). Genome-wide association studies have consistently identified the rs16969968 polymorphism in the CHRNA5 gene as a major genetic risk factor for development of nicotine dependence. This single nucleotide polymorphism (SNP) results in an Asp398Asn substitution, impairing nAChR function and increasing susceptibility to nicotine addiction. Pharmacological modulation of $\alpha 5$ -containing nAChRs represents a promising therapeutic strategy. However, achieving functional heterologous expression of these receptors in recombinant cell lines has been a longstanding challenge, hindering high-throughput drug screening and detailed biophysical characterization. This limitation has significantly slowed the development of targeted therapies for nicotine addiction and related disorders. To address this challenge, we conducted a comprehensive genome-wide cDNA expression screen to identify proteins that facilitate the functional assembly and surface expression of $\alpha 5$ -containing nAChRs. We discovered two critical proteins, TMIE (Transmembrane Inner Ear) and FAM163B (Family with Sequence Similarity 163 Member B), as essential for the functional expression of $\alpha 5$ -containing receptors. Our findings demonstrate that co-expression of TMIE or FAM163B with $\alpha 2\beta 2\alpha 5$ subunits enhances nicotine potency and efficacy by enabling efficient incorporation of the $\alpha 5$ subunit into the receptor complex. Notably, FAM163B has been genetically linked to nicotine addiction, further underscoring its physiological significance. This discovery overcomes a key bottleneck in the field, providing a functional high-throughput drug screening assay for $\alpha 5$ -

containing nAChRs. Our findings not only advance the understanding of nAChR assembly and function but also pave the way for the development of novel therapeutic agents targeting $\alpha 5$ -containing nAChRs to treat nicotine addiction.

Disclosures: **S. Gu:** A. Employment/Salary (full or part-time): Rapport Therapeutics, Inc. **D. Bredt:** A. Employment/Salary (full or part-time): Rapport Therapeutics, Inc.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.02/B10

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

Support: NIH R01 HL 146833-05

Title: Hypertension enhances intraganglionic cholinergic collateral connections

Authors: ***M.-H. LI**¹, K. KOH¹, S. L. INGRAM², M. C. ANDRESEN¹, B. A. HABECKER¹;
¹Oregon Hlth. & Sci. Univ., Portland, OR; ²Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: The autonomic nervous system plays a critical role in the pathophysiology of cardiac disease, including hypertension (HT). Cardiac sympathetic overactivation is a major feature of heart failure. However, the factors that contribute to sympathetic hyperactivity in disease are not well understood. We previously described excitatory cholinergic collateral synaptic connections between sympathetic ganglion neurons. Further, we discovered that angiotensin II (AngII) induced HT increases these cholinergic collateral connections during sustained sympathetic hyperactivity. In this study, we investigate the potential mechanism(s) underlying AngII HT induced hyperactivity in stellate ganglion (SG) neurons. We examined the properties of synaptic currents in SG neurons using whole-cell voltage-clamp recordings after one week of HT induced by peripheral AngII infusion. Graded shocks to the inferior cardiac nerve (iCN) evoked retrogradely conducted action current in cardiac postganglionic neurons. Stimulation of iCN evokes EPSCs with high latency jitter (polysynaptic events) and low jitter (mono synaptic events). AngII treatment increases the number of high jitter EPSCs compared to recordings from saline-treated mice, indicating more polysynaptic events. Consistent with more polysynaptic connections, a single stimulation generated more EPSCs in neurons from AngII-treated compared to saline-treated mice. Our results suggest that AngII HT increases sympathetic synaptic activity, which may contribute to the sustained sympathetic hyperactivity characteristic in cardiovascular disease. Current studies are testing whether stellate glia cells (SGCs) contribute to sympathetic hyperactivity observed in AngII HT.

Disclosures: **M. Li:** None. **K. Koh:** None. **S.L. Ingram:** None. **M.C. Andresen:** None. **B.A. Habecker:** None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.03/B11

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

Title: Mechanistic Insights into Rabies Glycoprotein Interaction with Nicotinic Receptors

Authors: *S. AKABERI¹, P. SAPKOTA², K. SHARMA³, M. K. SCHULTE⁴;

¹Biomed. and Pharmaceut. Sci., Idaho State Univ., Boise, ID; ²Biomed. and Pharmaceut. Sci.,

³Idaho State Univ., Pocatello, ID; ⁴Grad. Educ., Cummings Sch. of Vet. Med. at Tufts Univ., Grafton, MA

Abstract: Rabies virus remains nearly 100% fatal following symptom onset, with no effective treatment beyond prophylaxis. The rabies virus glycoprotein whole ectodomain (RABV-G) facilitates neuroinvasion, in part through its interaction with neuronal nicotinic acetylcholine receptors (nAChRs). It has been previously reported that short peptides derived from RABV-G are inhibitors of neuronal nAChRs. To further explore this inhibition, we produced recombinant proteins of the whole ectodomain of RABV-G. Proteins were produced in COS-7 cells, purified using IMAC and characterized using SDS-PAGE, Western blot, and LC-MS. Surface plasmon resonance (SPR) confirmed direct binding of the whole ectodomain of RABV-G variants to α 7-nAChBP. Using two-electrode voltage clamp recordings on *Xenopus laevis* oocytes expressing human α 4 β 2 or α 7 nAChRs, pathogenic variants of RABV-G, 183P and 183A, were found to inhibit acetylcholine induced currents. In contrast, a non-pathogenic variant, 196D, potentiated acetylcholine currents by ~60%. Both inhibition and potentiation were determined to be allosteric.

RABV-G is known to undergo a pH-dependent conformational change, shifting from a compact, pre-fusion conformation at neutral pH (7.4) to an elongated, post-fusion conformation at acidic pH (6.5). The pre-fusion conformation is thought to be the active, invasive conformation. In order to determine which conformation was involved in nAChR inhibition or potentiation, we tested RABV-G function at both pH 6.5 and pH 7.4. In *Xenopus* oocytes both the inhibitory effects of 183P and 183A, and the potentiating effects of 196D, were only observed at pH 7.4 and were abolished at pH 6.5. Thus, the presumed active conformation of the RABV-G is also the conformation that binds to neuronal nAChRs. The capability for a non-pathogenic virus (196D) to potentiate rather than inhibit receptors suggests a potential therapeutic strategy based on receptor modulation.

Disclosures: S. Akaberi: None. P. Sapkota: None. K. Sharma: None. M.K. Schulte: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.04/B12

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

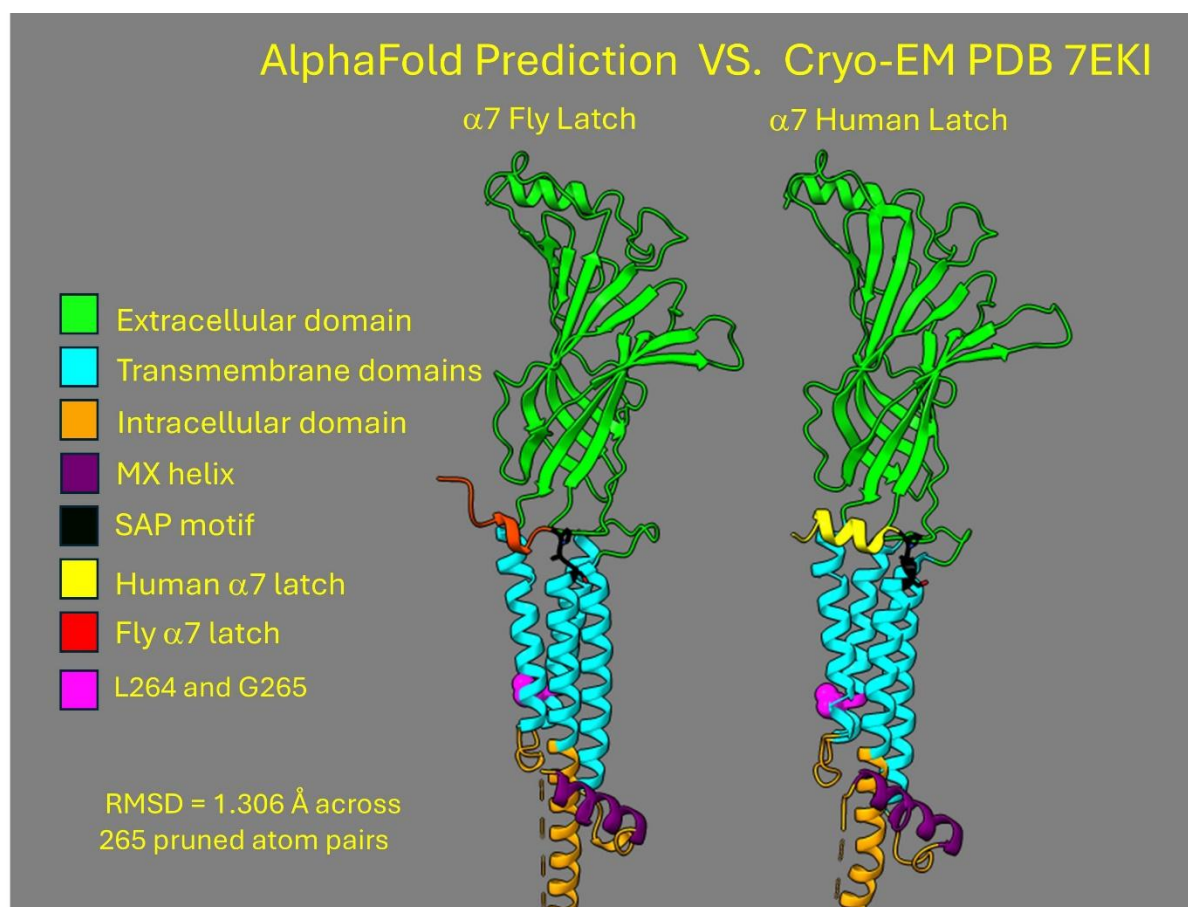
Support: Consulting

Title: Mutational analysis of $\alpha 7$ nicotinic receptor assembly: M2 and the latch

Authors: ***R. H. LORING**¹, A. LOKHANDE², M. TALEGAONKAR², J. VELMURUGAN², S. TEFERI²;

¹Pharmaceut. Sci., ²Northeastern Univ., Boston, MA

Abstract: How surface receptors fold and assemble is not understood even though they bind neurotransmitters and a wide variety of drugs. $\alpha 7$ Nicotinic receptors ($\alpha 7$ nAChRs) require chaperones NACHO or RIC3 to assemble and express on BOSC23 cell surfaces (measured by α -bungarotoxin binding). In contrast, chimeric proteins consisting of serotonin 5HT3 transmembrane domains (TMDs) and $\alpha 7$ nAChR extracellular and intracellular domains do not. Kweon et al. (PMID 32783947) report that swapping $\alpha 7$ /5HT3 residues in TMD2 (M2 residues L264F & G265K) blocked NACHO action, but we find that mutations L264A or G265A give different results. To further investigate, replacing 5HT3 M2 sequence RVSFK in $\alpha 7$ -5HT3 chimera with the $\alpha 7$ M2 sequence KISLG significantly blocks expression which NACHO and RIC3 cannot rescue. Conversely, replacing $\alpha 7$ M2 with a 5HT3 sequence including L264F & G265K completely blocked expression with no chaperone rescue. Therefore, although alanine substitutions retain some activity, L264 & G265 in M2 are important residues determining $\alpha 7$ nAChR assembly. Additional DNA constructs are under investigation. The $\alpha 7$ nAChR C-terminal α -helix (the “latch”, PMID 33735609) is highly conserved among vertebrates, but not invertebrates, whereas the ser-ala-pro (SAP) motif just prior to the latch is conserved from humans to worms (PMID 35889400). We find that the proline+latch combination allows expression in $\alpha 7$ -5HT3 chimeras without chaperones, but that adding any other part of the SAP motif blocks expression. To further investigate the role of the latch, we substituted human $\alpha 7$ latch sequence NFVEAVSKDFA with a fruit fly latch sequence HFIVSGVRG, which is predicted by Alphafold2 to be only a partial α -helix. Fly latch expression in human $\alpha 7$ nAChR was comparable to native human $\alpha 7$ nAChR in the presence of NACHO enhanced by RIC3. However, we saw variable results substituting the highly polar AlfaTag helix SRLEEELRRRLTE for the human $\alpha 7$ nAChR latch. Thus, the exact sequence of the latch is not a determining factor in $\alpha 7$ nAChR expression as long as the proline is present.



Disclosures: R.H. Loring: None. A. Lokhande: None. M. Talegaonkar: None. J. Velmurugan: None. S. Teferi: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.05/B13

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

Support: NCN OPUS-2021/41/B/NZ7/03101

Title: Development of specific nanobodies targeting the $\alpha 4$ subunit of nicotinic acetylcholine receptor

Authors: *W. A. NOWAK, D. NEMECZ, Á. NEMECZ;
Biochem., Nicolaus Copernicus Univ., Torun, Poland

Abstract: Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels, crucial for rapid chemical-to-electrical signal transduction. The human neuronal nAChRs are composed of α ($\alpha 2$ - $\alpha 7$) and β ($\beta 2$ - $\beta 4$) subunits, which can either form homopentamers, in the case of the $\alpha 7$ -nAChR, or heteropentamers. The $\alpha 4\beta 2$ -nAChR is the most prevalent subtype expressed in the central nervous system, which assembles in an α - β - α - β -X orientation where X may be either $\alpha 4$, $\beta 2$, or an “accessory” $\alpha 5$ subunit. Due to their widespread distribution in the brain, the $\alpha 4\beta 2$ -nAChRs are associated with cognitive functions, such as learning, memory, attention, pain, anxiety, reward, and addiction. In addition to their role in nicotine addiction, dysfunction of these nAChRs is implicated in neurological disorders such as Alzheimer’s disease, Parkinson’s disease, depression, and epilepsy. However, the receptor’s complex oligomeric composition and low stability when purified from membranes poses a problem in studying the different stoichiometries.

In an attempt to address this problem, two chimeric soluble proteins were created using an acetylcholine binding protein (AChBP), a soluble homolog of the extracellular domain of human nAChRs that have so far been found in mollusks, arachnids, and anilids. In this project, the *Aplysia californica* AChBP was used to mutate the apical domain to match that of the nAChR (Ap $\alpha 4$ -nAChR-*AcAChBP*), as well as an $\alpha 4\alpha 4$ -nAChR-*AcAChBP*, which mimics the ligand-binding interface between the $\alpha 4/\alpha 4$ subunits. Both of these chimeric constructs were used to generate and develop specific nanobodies against the $\alpha 4$ -nAChR subunit.

The developed chimeric constructs, as well as specific nanobodies, provide valuable tools for the structural and functional analysis of $\alpha 4\beta 2$ -nAChRs, and more specifically the ($\alpha 4$)₃($\beta 2$)₂-nAChRs. These tools may also serve as a potential therapeutic agent in treating CNS disorders associated with nAChR dysfunction.

Disclosures: W.A. Nowak: None. D. Nemecz: None. Á. Nemecz: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.06/B14

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

Support: NIH Grant R35 GM136430

Title: Functional expression and pharmacological characterization of homomeric human $\alpha 10$ nAChRs

Authors: *L. AZAM¹, B. TEKARLI¹, A. J. HONE^{1,3}, J. M. MCINTOSH^{1,2,4};

¹Sch. of Biol. Sci., ²Psychiatry, Univ. of Utah, Salt Lake City, UT; ³Mirecc, ⁴George E. Whalen Veterans Affairs Med. Ctr., Salt Lake City, UT

Abstract: Mammalian nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels composed of α ($\alpha 1$ - $\alpha 7$, $\alpha 9$, $\alpha 10$) and β ($\beta 1$ - $\beta 4$) subunits to form hetero or

homomeric isoforms. Subtypes of nAChRs are found within both the peripheral and central nervous systems and may display unique pharmacological and physiological properties based on subunit composition. The $\alpha 9$ and $\alpha 10$ subunits were initially characterized in cochlear hair cells and subsequently function was demonstrated in immune cells, where $\alpha 9/\alpha 10$ subunit-containing nAChRs form part of the cholinergic anti-inflammatory pathway. Previously it was believed that homomeric nAChRs are formed by only $\alpha 7$ or $\alpha 9$, but not $\alpha 10$, nAChR subunits. This determination was based on the observation that when nAChR subunit cRNA is injected into *Xenopus* oocytes, the $\alpha 10$ subunit alone shows little or no functional expression. In contrast, the $\alpha 10$ subunit readily forms a heteromer with the $\alpha 9$ subunit. Recently, we and others found that exposure to certain alkaloids, such as strychnine, potentiates the functional expression of $\alpha 10$ homomers in *Xenopus* oocytes and mammalian cell lines. Enhanced function of $\alpha 9\alpha 10$ nAChRs has also been observed in HEK cells when co-expressed with chaperones that are found in cochlear tissue. Here, we demonstrate the ability of the human $\alpha 10$ subunit to form functional homomeric receptors when co-expressed with resistance to inhibitors of cholinesterase 3 (RIC-3) and TMEM132e, two chaperones that are found in immune and cochlear hair cells, respectively. In addition, a gain-of-function mutant of the $\alpha 10$ subunit ($\alpha 10V13'T$) will express as a homomer in the absence of a chaperone protein. $\alpha 10$ nAChR homomers have a unique pharmacological profile with sensitivity to α -bungarotoxin but insensitivity to conopeptides that potentially block $\alpha 9\alpha 10$ nAChRs. Thus, $\alpha 10$ subunits will self-assemble into homomers with function that is significantly enhanced by either exposure to strychnine or co-expression with a chaperone.

Disclosures: L. Azam: None. B. Tekarli: None. A.J. Hone: None. J.M. McIntosh: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.07/B15

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

Support: NIH IDaho INBRE REsearch Grant

Title: Sar guided discovery of positive allosteric modulators of $\alpha 9/\alpha 10$ nicotinic acetylcholine receptors for the treatment of hidden hearing loss

Authors: *P. SAPKOTA¹, S. AKABERI², J. OMAN², S. PASHIKANTI², K. SHARMA², S. ZELEKE², M. K. SCHULTE³;

¹Biomed. and Pharmaceut. Sci. Dept., ²Idaho State Univ., Pocatello, ID; ³Grad. Educ., Cummings Sch. of Vet. Med. at Tufts Univ., Grafton, MA

Abstract: Hearing Loss affects approximately 18% of the world's population. Hidden hearing loss (HHL), characterized by hearing difficulties despite normal thresholds, impacts an even larger population with no effective treatment yet identified (Liu, Stohl, & Overath, 2024). The $\alpha 9/\alpha 10$ nicotinic acetylcholine receptors (nAChRs) present in cochlear outer hair cells are a

promising molecular target for noise-induced HHL and age-related hearing loss, given their critical role in regulating synaptic transmission between efferent medial olivocochlear fibers and outer hair cells (Boero et al., 2018). We aim to develop potent and selective positive allosteric modulators of $\alpha 9/\alpha 10$ nAChRs through structure-activity relationship (SAR) studies of ascorbate derivatives. Synthetic analogs of ascorbate were screened utilizing electrophysiological assays in *Xenopus laevis* oocytes expressing recombinant $\alpha 9/\alpha 10$ nAChRs. We evaluated these analogs for their ability to potentiate acetylcholine (ACh) - evoked currents and determined concentration-dependent efficacy (EC_{50}). Notably, a novel ascorbate analog, 3-O-propargyl-Acetonide-L-Ascorbate potentiated ACh current in $\alpha 9/\alpha 10$ nAChRs with an EC_{50} value of 0.08 μM representing a nearly 3000-fold increase in potency compared to ascorbate ($EC_{50} > 300 \mu M$), despite exhibiting lower antioxidant activity. To elucidate the binding interactions, we designed a three-dimensional homology model of $\alpha 9/\alpha 10$ nAChRs using Schrodinger's Maestro and performed molecular docking of active ascorbate analogs. Our findings suggest that a transmembrane pocket beneath M2-M3 loop may serve as a potential binding site for PAMS of these receptors although additional sites are currently under investigation. This work contributes to targeted drug discovery for hearing disorders addressing a unmet need in hearing loss therapeutics. Further studies on receptor selectivity, potentiation mechanism, binding interactions, and pharmacokinetic studies are essential to validate their potential for therapeutic activity.

Disclosures: P. Sapkota: None. S. Akaberi: None. J. Oman: None. S. Pashikanti: None. K. Sharma: None. S. Zeleke: None. M.K. Schulte: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.08/B16

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

Support: GM136430

Title: Peptides containing amino-acid sequences of the SARS-CoV-2 spike protein are antagonists of $\alpha 7$ and $\alpha 9\alpha 10$ nicotinic acetylcholine receptors and modulate interleukin-1 β release from human monocytes

Authors: *A. J. HONE¹, K. RICHTER³, Z. RIAZ², J. M. WAKKURI¹, B. TEKARLI², J. GAJEWIAK², V. GRAU⁴, J. MCINTOSH⁵;

²Sch. of Biol. Sci., ¹Univ. of Utah, Salt Lake City, UT; ³Dept. of Gen. and Thoracic Surgery,

⁴Justus-Liebig Univ. of Giessen, Giessen, Germany; ⁵Univ. Utah, Salt Lake City, UT

Abstract: Nicotinic acetylcholine receptors (nAChRs), particularly those subtypes containing $\alpha 7$, $\alpha 9$, and/or $\alpha 10$ subunits, have been implicated in the hyperinflammation associated with SARS-CoV-2 infection. The SARS-CoV-2 spike-protein contains a sequence of polybasic

amino-acids that forms a cleavage site for the enzyme furin. This furin cleavage-site (FCS) sequence is similar to peptide neurotoxins found in the venom of elapid snakes and marine cone snails that target $\alpha 7$ and $\alpha 9\alpha 10$ subtypes and thus has been postulated to interact with and inhibit immune-cell expressed nAChRs. Inhibition of immune cell nAChRs results in excessive release of inflammatory cytokines which is a feature of SARS-CoV-2 pathology including the associated cytokine storm. Dissecting the interaction between the spike protein and nAChRs containing $\alpha 7$, $\alpha 9$, and/or $\alpha 10$ subunits has been challenging due to the chemical properties of in vitro produced spike-protein constructs. Here we describe the design and synthesis of a series of peptides with amino-acid sequences corresponding to the FCSs of five SARS-CoV-2 variants. The activity of these peptides was assessed by two-electrode voltage-clamp electrophysiology of *Xenopus laevis* oocytes heterologously expressing human nAChRs. Potency of the wild-type (WT) variant (B.1) for $\alpha 7$ and $\alpha 9\alpha 10$ nAChRs was low. By contrast, higher potency was observed for peptides that mimicked the evolution of the FCS in the Alpha (B.1.1.7), Delta (B.1.617.2), Omicron (B.1.1.529), and FLiRT (JN.1) variants. Of the five peptides tested, the most potent corresponded to that of FLiRT. The peptides' effects on release of the inflammatory cytokine interleukin-1 β (IL-1 β) were examined using human monocyte THP-1 cells. Inhibition of BzATP-stimulated IL-1 β release by acetylcholine was completely abrogated in the presence of the Omicron and FLiRT peptides. These results indicate that the FCS of the SARS-CoV-2 spike-protein may interact with $\alpha 7$ and $\alpha 9\alpha 10$ nAChRs expressed by immune cells, inhibit their control over inflammatory cytokine release, and contribute to the pathology associated with the cytokine storm.

Disclosures: A.J. Hone: None. K. Richter: None. Z. Riaz: None. J.M. Wakkuri: None. B. Tekarli: None. J. Gajewiak: None. V. Grau: None. J. McIntosh: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.09/B17

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

Support: 2023000CB0030
2023100CB0060

Title: Utilizing electrophysiology and molecular simulation to investigate the molecular mechanisms of quercetin modulating $\alpha 7$ nAChR in synergy with low-dose nicotine for ameliorating Alzheimer's disease

Authors: L. XU^{1,2}, Q. LI^{1,2}, *Y. LI^{1,3}, W. MU^{1,3}, J. ZHANG^{1,3}, X. LI^{1,3}, Y.-N. MA^{1,3}, Z. NI¹, H. CHEN^{1,2,3}, H. HOU^{1,2,3};

¹Beijing Life Sci. Acad., Beijing, China; ²China Natl. Tobacco Quality Supervision and Test Ctr., Zhengzhou, China; ³Key Lab. of Tobacco Biol. Effects, Zhengzhou, China

Abstract: The $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR), a crucial ligand-gated ion channel in the nervous system, is involved in regulating diverse physiological processes, including cognition and inflammation. Nicotine can exert neuroprotective effects, such as ameliorating Alzheimer's disease (AD), by activating $\alpha 7$ nAChR; however, its clinical application is limited by its addictive properties. Quercetin (Qu), as a positive allosteric modulator of $\alpha 7$ nAChR, may mitigate nicotine addiction when co-administered with low-dose nicotine for AD treatment. In this study, behavioral assessments in APP/PS1 mouse models of AD demonstrated that compared to nicotine or quercetin alone, combined administration of low-dose nicotine (0.1mg/kg) and quercetin (3mg/kg) significantly improved memory and spatial recognition (Barnes maze escape latency was significantly reduced, $p < 0.001$) and effectively decreased cerebral A β plaque load ($p < 0.05$). Furthermore, qRT-PCR results indicated that co-administration of quercetin and nicotine specifically upregulated $\alpha 7$ nAChR expression in the hippocampus ($p < 0.01$), whereas the expression of addiction-related receptors $\alpha 4\beta 2$, D1, and D2 showed no significant changes. Conversely, a high-dose nicotine group (0.5mg/kg) exhibited significant upregulation of all four addiction-related receptors ($p < 0.05$). These findings preliminarily suggest that this combination strategy can enhance nicotine's neuroprotective effects without increasing its addictive potential. Molecular docking and molecular dynamics simulations further revealed that quercetin stably binds to an allosteric site within the transmembrane domain of $\alpha 7$ nAChR. This binding induces a conformational shift towards an activated state, thereby enhancing the binding efficacy of nicotine to the orthosteric site, which may constitute the molecular basis for its synergistic action and addiction-reducing potential. Electrophysiological experiments demonstrated that quercetin significantly potentiated nicotine-induced $\alpha 7$ nAChR current responses ($p < 0.001$), confirming its positive allosteric modulatory activity on $\alpha 7$ nAChR. In summary, this research, through molecular modeling, electrophysiology, and animal behavior studies, reveals that quercetin, via allosteric modulation of $\alpha 7$ nAChR, enhances the neuroprotective effects of low-dose nicotine against AD without exhibiting addiction risk, thereby offering a novel therapeutic strategy for safer AD treatment.

Disclosures: L. Xu: None. Q. Li: None. Y. Li: None. W. Mu: None. J. Zhang: None. X. Li: None. Y. Ma: None. Z. Ni: None. H. Chen: None. H. Hou: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.10/B18

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

Support: R01DA043567
T32DA007027

Title: Functional effects of lynx1 on $\alpha 3\beta 4$ nicotinic receptor function are mediated by a unique subunit interface

Authors: *D. KNEISLEY¹, H. OH¹, Y. CAO³, W. IM³, J. M. MIWA³, P. WHITEAKER²;
¹Pharmacol. & Toxicology, ²Dept. of Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA; ³Biol. Sci., Lehigh Univ., Bethlehem, PA

Abstract: Smoking, maintained by nicotine-seeking behaviors, is the leading cause of preventable death worldwide. In the brain, nicotine acts on nicotinic acetylcholine receptors (nAChR). The $\alpha 3\beta 4$ -nAChR subtype mediates aspects of nicotine withdrawal by modulating activity of GABAergic neurons of the interpeduncular nucleus. The prototoxin lynx1 is also highly expressed in these neurons. Lynx1 allosterically diminishes $\alpha 3\beta 4$ -nAChR macroscopic responses and is most potent on the $(\alpha 3\beta 4)_2\alpha 3$ isoform, which uniquely contains an $\alpha 3/\alpha 3$ subunit interface. At the single-channel level, lynx1 decreases $(\alpha 3\beta 4)_2\alpha 3$ -nAChR conductance and shortens open bursts. Therefore, we investigated the $\alpha 3/\alpha 3$ site for its role in mediating lynx1 binding. Molecular dynamics simulations were used to identify residues at the $\alpha 3/\alpha 3$ interface where we hypothesized that lynx1 interacts, and these residues were individually mutated in an alanine-scanning approach. Sensitivity to lynx1 inhibition of the resulting mutants was assessed using two-electrode voltage clamp (TEVC) electrophysiology. These mutations were expected to decrease receptor sensitivity to lynx1 effects and several did, confirming that lynx1 effects are mediated by this site. However, in some cases we observed increased sensitivity to lynx1 instead, and all mutations diminished ACh-induced macroscopic function in the absence of lynx1. Combined, these observations suggest the presence of a third agonist binding site, located at the $\alpha 3/\alpha 3$ interface, at which lynx1 and ACh compete to bind. A selection of mutants with the most significant changes in lynx1 sensitivity from the TEVC studies were used for cell-attached single-channel patch clamp electrophysiology experiments in order to understand how mutations alter function of individual receptors. Mutation of a tyrosine residue in the $\alpha 3/\alpha 3$ interface, which would correspond to a critical agonist-binding residue in an orthosteric binding pocket, reduces burst durations and single-channel amplitudes compared to the wild-type (WT) receptor. These outcomes closely parallel those of lynx1 binding to a WT receptor, further supporting the presence of a third ACh binding site at the $\alpha 3/\alpha 3$ interface. Addition of lynx1 to the mutant receptor further reduced burst durations and single-channel amplitudes, suggesting that, in addition to competing with agonist binding, lynx1 binding at the $\alpha 3/\alpha 3$ site may exert a further negative allosteric effect upon the function of $(\alpha 3\beta 4)_2\alpha 3$ -nAChR. The $\alpha 3/\alpha 3$ interface may provide a promising target for future smoking cessation withdrawal therapies.

Disclosures: D. Kneisley: None. H. Oh: None. Y. Cao: None. W. Im: None. J.M. Miwa: None. P. Whiteaker: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.11/B19

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

Support: NINDS R16NS129676

Title: Assessment of (α 4)₃(β 2)₂ nicotinic acetylcholine receptor positive allosteric modulators in a 6-OHDA Zebrafish Model.

Authors: *K. APPIAH-POKU¹, N. PINHEIRO MENEGASSO², W. FELIX³, Y. NAZRUL¹, G. THAKUR³, A. K. HAMOUDA², B. BILL⁴;
²Pharmaceut. Sci. and Hlth. Outcomes, ¹Univ. of Texas at Tyler, Tyler, TX; ³Northeastern Univ., Boston, MA; ⁴Biol., The Univ. of Texas at Tyler, Tyler, TX

Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by motor dysfunction and other syndromic features caused by loss of striatal dopaminergic (DA) neurons. Current treatments focus on increasing DA synthesis to mitigate symptoms, but they do not cure PD suggesting a need for alternative therapeutics. Nicotinic acetylcholine receptors (nAChR) are expressed on the striatal DA neurons; and their activation leads to increases in dopamine concentration suggesting these receptors are potential druggable targets. Due to receptor promiscuity of nicotine as well as a lack of consistent results, receptor subunit specific drugs are being investigated. Positive allosteric modulators (PAMs) of the (α 4)₃(β 2)₂ nAChR represent a new class of receptor specific drugs that increase the affinity for acetylcholine thus increasing its activation potency. The (α 4)₃(β 2)₂ subtype is highly expressed in dopaminergic neurons and has been implicated in cognitive and motor modulation, making it a relevant therapeutic target in Parkinson's Disease. Our lab has previously optimized a 6-hydroxydopamine zebrafish model for assessing potential drugs using behavioral and molecular readouts. We hypothesized that these receptor specific PAMs would mitigate the behavioral and molecular phenotypes observed in our 6-hydroxydopamine (6-OHDA) model. The PAMs are chemical derivatives of CMPI (3-(2-chlorophenyl)-5-(5-methyl-1-(piperidin-4-yl)-1H-pyrazol-4-yl) isoxazole) that were selected based on their ability to potentiate (α 4)₃(β 2)₂ nAChR with and $EC_{50} < 1 \mu M$ in a *Xenopus* TEVC model. We assessed the toxicity *in vivo* by exposing zebrafish larvae, 3- or 4-days post fertilization (dpf), to the PAM for 24 hours then assessing viability and morphology at 6, 24, and 48 hours post initial exposure. Most PAMs were not toxic to larvae at concentrations corresponding to their EC_{50} ; however, toxicity was observed at higher concentrations for some compounds. Ongoing experiments to evaluate the effect of lead PAM candidates on 6-OHDA-exposed larvae specifically quantitating spontaneous activity (movement) and gene expression for biomarkers implicated in dopamine synthesis, mitochondrial health, and reactive oxygen species response.

Disclosures: K. Appiah-Poku: None. N. Pinheiro Menegasso: None. W. Felix: None. Y. Nazrul: None. G. Thakur: None. A.K. Hamouda: None. B. Bill: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.12/B20

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

Support: NINDS R16NS129676

Title: Substituted piperidines ($\alpha 4$)₃($\beta 2$)₂ nicotinic acetylcholine receptor positive allosteric modulators: In vitro pharmacology.

Authors: *N. E. SANCHEZ¹, J. GAONA³, W. FELIX⁴, N. PINHEIRO MENEGASSO², B. CEA¹, G. THAKUR⁴, A. K. HAMOUDA²;

²Pharmaceut. Sci. and Hlth. Outcomes, ¹Univ. of Texas at Tyler, Tyler, TX; ³The Univ. of Texas at Tyler, Tyler, TX; ⁴Northeastern Univ., Boston, MA

Abstract: Nicotinic acetylcholine receptors (nAChRs) play a crucial role in the pathogenesis of neurodegenerative diseases such as Parkinson's disease (PD). In PD, degeneration of dopaminergic and cholinergic neurons impairs neurotransmitter release, leading to cognitive and motor dysfunction. Current treatments provide only symptomatic relief, highlighting the need for novel therapeutic strategies. The ($\alpha 4$)₃($\beta 2$)₂ subtype of nAChRs is expressed on affected neurons, making it a promising druggable target for enhancing neurotransmitter release and providing neuroprotection. To explore the therapeutic potential of positive allosteric modulators (PAMs) of ($\alpha 4$)₃($\beta 2$)₂ nAChRs, we evaluated chemical derivatives of CMPI [3-(2-chlorophenyl)-5-(5-methyl-1-(piperidin-4-yl)-1H-pyrazol-4-yl)isoxazole]. We used two-electrode voltage-clamp recordings from *Xenopus laevis* oocytes expressing nAChRs with defined subunit compositions to screen new derivatives for PAM activity and to construct dose-response curves for lead compounds. We also evaluated the *in vitro* cytotoxicity of the CMPI derivatives using the MTT assay. Our results thus far establish that substitutions at the pyrazole ring of CMPI (e.g., to a thiazole in A12a or an imidazole in A12c and A12e) are tolerated within the $\alpha 4$ - $\alpha 4$ binding pocket and maintain selectivity for ($\alpha 4$)₃($\beta 2$)₂ (EC₅₀ for potentiation < 1 μ M) over ($\alpha 4$)₂($\beta 2$)₃ nAChRs. In contrast, modifications at the piperidine ring (e.g., to piperazine derivatives in GAT2227-GAT2230) are less tolerated, resulting in reduced or no PAM activity. Cell toxicity assays using HEK cells expressing $\alpha 4\beta 2$ nAChRs showed no toxicity of the CMPI derivatives at concentrations that potentiate ($\alpha 4$)₃($\beta 2$)₂ nAChRs. Among these, A12c exhibited no effect on cell viability at concentrations up to 100 μ M. The mode of binding for CMPI derivatives was investigated using computer-simulated docking and site-directed mutagenesis, which confirmed the extracellular $\alpha 4$ - $\alpha 4$ subunit interface as a potential binding site and identified key interactions between PAMs and amino acid residues. This study provides further evidence supporting the potential of PAMs acting at the $\alpha 4$ - $\alpha 4$ interface as a strategy to selectively target the ($\alpha 4$)₃($\beta 2$)₂ nAChR, a major subtype in the cortex. CMPI derivatives are currently being investigated in a PD-like zebrafish model, which is expected to provide evidence of *in vivo* efficacy and support their therapeutic potential for the treatment of neurodegenerative diseases.

Disclosures: N.E. Sanchez: None. J. Gaona: None. W. Felix: None. N. Pinheiro Menegasso: None. B. Cea: None. G. Thakur: None. A.K. Hamouda: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.13/B21

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

Support: NIH P20GM103395
NIH 5R16GM150455

Title: Regulation of $\alpha 4\beta 2$ nicotinic acetylcholine receptor trafficking to the plasma membrane by visinin-like protein-1

Authors: *S. M. SUAREZ¹, M. M. WELTZIN²;

¹Univ. of Alaska, Fairbanks, AK; ²Chem. and Biochem., Univ. of Alaska Fairbanks, Fairbanks, AK

Abstract: Neurological conditions, like nicotine use disorder (NUD), are associated with disruptions in brain cholinergic tone, partly due to dysregulation of $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs). The predominant $\alpha 4\beta 2$ nAChR subtype occurs in two isoforms with high and low sensitivity to agonist (HS and LS, respectively). Visinin-like protein-1 (VILIP-1) is an endogenous calcium sensor that attenuates $\alpha 4\beta 2$ nAChR function, perhaps by interacting with the $\alpha 4$ subunit. We hypothesize that, when in high abundance, VILIP-1 modulates $\alpha 4\beta 2$ nAChR isoform expression by reducing $\alpha 4$ subunit trafficking to the plasma membrane. To assess VILIP-1 modulation of plasma membrane expression of $\alpha 4\beta 2$ nAChRs, the $\alpha 4$ and $\beta 2$ genes were C-terminally tagged with pH-sensitive fluorescent markers Superecliptic pHluorin (SEP) or pHuji, respectively. VILIP-1 was N-terminally tagged with mTagBFP2, and a VILIP-1 negative control group was transfected with mTagBFP2 in the absence of VILIP-1 DNA to identify cells triple-transfected. Two-electrode voltage clamp (TEVC) electrophysiology experiments were performed to ensure each tagged protein functioned similarly to the untagged proteins. To quantify changes in VILIP-1-driven trafficking of $\alpha 4\beta 2$ nAChRs, neuronal-like mammalian N2a cells were cultured and transiently transfected with fluorescently tagged $\alpha 4$, $\beta 2$, and VILIP-1 or mTAGBFP2 DNAs. At pH 7.4, the total cellular expression of tagged proteins was captured in live N2a cells (37°C) using an Olympus FLUOVIEW FV10i confocal laser scanning microscope. Following, a pH=5.4 extracellular media change occurred to quench the pH-sensitive tags expressed on the plasma membrane, and the same cells were imaged. ImageJ was used to evaluate the acquired images, and corrected total cell fluorescence (CTCF) analysis was used to quantify cellular fluorescence. To calculate the relative surface expression of each subunit, the CTCF intensity of each cell at pH 7.4 was subtracted from the CTCF of the same cell at pH 5.4. Moderate expression of VILIP-1 enhanced the $\alpha 4$ subunit CTCF intensity. In contrast, a five-fold increase in VILIP-1 did not enhance plasma membrane expression, suggesting a gene dose-dependent effect on tracking of the $\alpha 4$ nAChR subunit to the plasma membrane. These outcomes complement our functional electrophysiology data. Our findings advance the understanding of intrinsic control mechanisms regulating nAChR function and expression and may contribute to the improvement of nicotine use cessation therapies.

Disclosures: S.M. Suarez: None. M.M. Weltzin: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.14/B22

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

Support: Z01ES090089

Title: An integrated paradigm for investigation of ventral subiculum neural modulation on Innate versus learned Threat Processing

Authors: *S. WANG^{1,2}, K. D. STEVANOVIC³, J. D. CUSHMAN³, J. L. YAKEL³;
¹NIEHS, RTP, NC; ²Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Rtp, NC; ³Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., RTP, NC

Abstract: The ventral subiculum(vSub) serves as the relay center gating the information exchange between the ventral hippocampus and brain regions involved in threat processing, including the amygdala, prefrontal cortex, and hypothalamus. Yet, the precise function of vSub in threat processing remains poorly understood. In addition, the vSub receives dense cholinergic input from the basal forebrain. Prior studies have shown that acetylcholine (ACh) modulates vSub neuronal activity ex vivo, and that ACh signaling in the vSub responds to both innate and conditioned threats in vivo. However, whether ACh signaling in the vSub differentially regulates innate versus learned defensive behavior and how ACh signaling interacts with local neural circuits during threat processing. To address these questions, we developed a closed-loop behavioral paradigm to tests both innate and learned defensive responses in the same animals. Mice were exposed to naïve tones or expanding black circle animations overhead mimicking predator attacks (looming stimulus) in two consecutive days. They then underwent fear conditioning in a novel context associating the tone to a different aversive stimulus (.7mA foot-shock). After conditioning, mice were returned to the original arena to test responses to the looming or tone stimuli. Simultaneously, we recorded acetylcholine dynamics and local circuit activity in the vSub using a GRAB_{ACh} sensor and an integrated probe enabling fiber photometry and local field potential (LFP) recording during behavior. This setup allows us to track the ACh signaling and monitor its interaction with local neural activity at different stages of threat processing. We found that both looming stimuli and conditioned tone, but not the naïve tone effectively triggered escaping behavior. ACh levels in the vSub increased in response to looming stimuli, followed by a prolonged decrease. In contrast, the conditioned tone induced a larger ACh increase to naïve tone, without a post-stimulus decrease. Repeated looming stimuli elicited more robust escape behavior than conditioned tone, though post-stimulus freezing levels were comparable. Notably, the magnitude of ACh increase didn't differ significantly between the two stimuli. These results showed that our modified paradigm provides a robust platform to study neuromodulation in threat processing. Moreover, our data suggested that ACh signaling contributes to both innate and learned threat processing, with some different patterns of response. Further analysis on the LFP recording and functional manipulation (e.g. optogenetics) on ACh release in vSub are needed to dissect the role of ACh in threat processing.

Disclosures: S. Wang: None. K.D. Stevanovic: None. J.D. Cushman: None. J.L. Yakel: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.15/B23

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

Support: NIH Grant (R01DA059985)

Title: Electrophysiological Characterization and Computational Prediction of (2-Amino-5-keto)thiazole-based Positive Allosteric Modulators of $\alpha 4\beta 2$ Nicotinic Acetylcholine Receptors

Authors: *K. S. ABDELWAHED¹, W. A. FELIX², J. GAONA¹, N. E. SANCHEZ¹, P. GADEKAR², G. A. THAKUR², A. K. HAMOUDA¹;

¹Dept. of Pharmaceut. Sci. and Hlth. Outcomes, The Univ. of Texas at Tyler, Tyler, TX; ²Dept. of Pharmaceut. Sci., Northeastern Univ., Boston, MA

Abstract: Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels that regulate neurotransmission and synaptic plasticity in the central nervous system. The $\alpha 4\beta 2$ subtype, a predominant form in the brain, exists in two stoichiometric isoforms -high-sensitivity (HS; $(\alpha 4)_2(\beta 2)_3$) nAChRs and low-sensitivity (LS; $(\alpha 4)_3(\beta 2)_2$) nAChRs- and plays a key role in cognitive function and nicotine addiction-related behavior, making it a promising target for neuropsychiatric drug development. In this work, we report on the design, synthesis, pharmacological evaluation, and computational modeling of a novel series of compounds structurally derived from previously reported nAChR positive allosteric modulators (PAMs) LY1078733 and LY2087133 (Broad LM et al. *J Pharmacol Exp Ther.* 2006). The functional activity of newly synthesized compounds was assessed using two-electrode voltage-clamp (TEVC) recordings in *Xenopus laevis* oocytes expressing $\alpha 4\beta 2$ nAChRs. Compounds were tested at 1 μ M co-applied with 10 μ M ACh on both LS and HS nAChR isoforms. The potentiation effect of these compounds was quantified relative to the effect of the agonist alone and to the effect of the agonist co-applied to 1 μ M LY1078733. Structure-activity relationship (SAR) analysis revealed that modifications at the fluorophenyl and thiazole regions of the parent scaffolds (e.g., GAT2240 and GAT2246) were well tolerated and maintained PAM effectiveness at both HS and LS $\alpha 4\beta 2$ nAChR isoforms. In contrast, alterations at the benzodioxole group of LY2087133 and the tolyl group of LY1078733 dramatically decrease PAM activity at $\alpha 4\beta 2$ nAChRs. Computational molecular docking studies using the CDOCKER algorithm in Discovery Studio provided further support. Simulations were conducted using 20 Å binding spheres centered along the vertical axis of the $\alpha 4:\beta 2$ and $\beta 2:\alpha 4$ transmembrane subunit interfaces in both isoforms (PDBs# 6CNJ for HS and 6CNK for LS). Together, these findings highlight the potential of (2-amino-5-keto) thiazole-based nAChR PAMs as scaffolds for developing $\alpha 4\beta 2$ nAChR modulators. These results enhance our ability to introduce structural modifications at the benzodioxole group and the tolyl group as a strategy for rational drug design of either positive or negative allosteric $\alpha 4\beta 2$ nAChR modulators.

Disclosures: K.S. Abdelwahed: None. W.A. Felix: None. J. Gaona: None. N.E. Sanchez: None. P. Gadekar: None. G.A. Thakur: None. A.K. Hamouda: None.

Poster

PSTR005: Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR005.16/B24

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

Support: NIH Grant (R01DA059985)
NIH Grant (R16NS129676)

Title: Revisiting Computational Predictions of Ligand Binding Modes at the $\alpha 4:\alpha 4$ Extracellular Interface in $(\alpha 4)3(\beta 2)2$ Nicotinic Acetylcholine Receptor

Authors: *E. G. PHELPS, K. S. ABDELWAHED, A. K. HAMOUDA;
Dept. of Pharmaceut. Sci. and Hlth. Outcomes, The Univ. of Texas at Tyler, Tyler, TX

Abstract: The $\alpha 4$ and $\beta 2$ nicotinic acetylcholine receptor (nAChR) subunits assemble into structurally, functionally, and pharmacologically distinct stoichiometries, most notably the high-sensitivity $(\alpha 4)2(\beta 2)3$ and low-sensitivity $(\alpha 4)3(\beta 2)2$ isoforms (HS and LS, respectively). The LS is the predominant $\alpha 4\beta 2$ subtype in the cortex and is known to contribute to complex brain functions including cognition and memory. Unlike HS, the LS features a unique $\alpha 4:\alpha 4$ extracellular interface, which acts as a third, non-canonical agonist binding site, in addition to the two canonical $\alpha 4:\beta 2$ orthosteric sites. This $\alpha 4:\alpha 4$ site has emerged as a functionally relevant site for modulating agonist efficacy and allosteric interactions. Previous studies have shown that only agonists with small molecular volume, such as ACh, can occupy the $\alpha 4:\alpha 4$ site and exert full efficacy at the $(\alpha 4)3(\beta 2)2$ nAChR, whereas agonists with larger molecular volume such as TC-2559 are excluded from binding. Furthermore, positive allosteric modulators (PAMs) such as CMPI and NS9283 have demonstrated selective potentiation of the LS stoichiometry by binding at $\alpha 4:\alpha 4$ extracellular interface. Earlier computational studies to predict agonists and PAMs binding at the $\alpha 4:\alpha 4$ extracellular interface relied on homology models to generate LS isoform from other nAChRs or ACh binding proteins. However, the recent availability of high-resolution 3D structures of LS $(\alpha 4)3(\beta 2)2$ nAChR—including PDBs: 6CNK (nicotine-bound), 8ST1 (with ACh and calcium), and 8ST2 (with ACh alone)—now enables more accurate prediction of ligand binding using experimentally resolved receptor conformations. This study revisits previous computational predictions for agonists binding/lack of binding at the $\alpha 4:\alpha 4$ extracellular interface to determine agonist selectivity, mode of binding, and key interactions between agonists and amino acids contributing to the $\alpha 4:\alpha 4$ agonist bind site. We also evaluating the binding modes of LS-selective nAChR PAMs (CMPI and NS9283) at the $\alpha 4:\alpha 4$ extracellular interface. Our preliminary results show that all agonists we tested adopted favorable poses at the agonist pocket at the $\alpha 4:\beta 2$ orthosteric sites as well as the $\alpha 4:\alpha 4$ agonist bind site. CMPI and NS9283 successfully dock at the $\alpha 4:\alpha 4$ extracellular interface in the presence and absence of co-

crystallized agonists—nicotine (6CNK) and ACh (8ST1, 8ST2). We expect structural data obtained via these computational predictions to facilitate the development of stoichiometry-specific ligands targeting the $\alpha 4:\alpha 4$ extracellular interface and support the pharmacological potential of PAMS for treating neuropsychiatric conditions involving brain nAChRs.

Disclosures: E.G. Phelps: None. K.S. Abdelwahed: None. A.K. Hamouda: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.01/B25

Topic: B.04. Synaptic Transmission

Support: JSPS KAKEN 25H00434
AMED BrainMind2 JP25wm0625101
JST CREST JPMJCR21E2
JST FOREST JPMJFR231T
JSPS KAKEN 23K14285

Title: Mechanical Control of the Number of SNARE Assemblies per Synaptic Vesicle for Release Probability

Authors: *Y. MORIMOTO, H. OKAZAKI, F. ETO, H. UCAR, H. KASAI;
Intl. Res. Ctr. for Neurointelligence (WPI-IRCN), UTIAS, The Univ. of Tokyo, Tokyo, Japan

Abstract: The pre-assembly of SNARE proteins is critical for the ultrafast release of neurotransmitters. Although the number of SNARE complexes per synaptic vesicle is a key determinant of release probability (Pv), it remains unclear whether this number is dynamically regulated by physiological stimuli. We previously demonstrated that mechanical force generated by postsynaptic spine enlargement enhances presynaptic neurotransmitter release, concomitant with increased SNARE complex formation, as revealed by FRET-FLIM analysis of mTurquoise2-Syntaxin1A and ShadowG-VAMP2 interactions in organotypic hippocampal slice cultures (Ucar et al., Nature 2021). In the present study, we further investigated the mechanical regulation of presynaptic function using dissociated rat hippocampal neuron cultures. Neurons were co-transfected with iGluSnFR and CsChrimsonR using Cre/DIO lentiviral vectors driven by the CaMKII (0.4) promoter, enabling sparse labeling for precise optogenetic stimulation and real-time monitoring of glutamate release from individual presynaptic terminals. Mechanical stimulation was applied through three independent methods: glass pipette pressure, application of 20 mM sucrose, or spine enlargement via the chemogenetic probe SYNCit-K (Sawada et al., Science 2024). Quantal analysis of glutamate release amplitude from single presynaptic terminals revealed that mechanical pressure significantly increased Pv of individual vesicles without altering the number of functional release sites (N). Simultaneous FRET-FLIM measurements of SNARE complex formation demonstrated that Pv positively correlated with the

SNARE binding fraction, which was also elevated upon mechanical stimulation. Notably, this mechanical effect saturated at a Pv of 0.8, suggesting that the maximal number of SNARE assemblies per vesicle is fixed. These findings indicate that the number of SNARE complexes per vesicle is a dynamically regulated parameter that directly controls release probability, and such regulation is physiologically driven by dendritic spine enlargement. We are currently investigating the temporal dynamics underlying this mechanically induced modulation of release probability.

Disclosures: Y. Morimoto: None. H. Okazaki: None. F. Eto: None. H. Ucar: None. H. Kasai: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.02/B26

Topic: B.04. Synaptic Transmission

Support: JSPS KAKEN 25H00434
AMED BrainMind2 JP25wm0625101
JST CREST JPMJCR21E2

Title: Mechanical actions on presynaptic terminals induce vesicle dispersion and enhance vesicle mobilization in rat hippocampal pyramidal neurons

Authors: *F. ETO, H. UCAR, H. OKAZAKI, Y. MORIMOTO, H. KASAI;
Intl. Res. Ctr. for Neurointelligence (WPI-IRCN), UTIAS, The Univ. of Tokyo, Tokyo, Japan

Abstract: Synaptic vesicles (SVs) are clustered in presynaptic terminals by synapsins, which cross-link vesicles and potentially form a biological condensate. It has recently been reported that spine enlargement exerts mechanical actions on presynaptic terminals, facilitating neurotransmitter release probability for 20-30 minutes (Ucar *et al.*, *Nature* 2021). Here, we monitored SV clusters using two-photon photoactivation of PAGFP-VAMP2 and observed marked dispersion of SV clusters due to mechanical pressures induced by spine enlargement triggered by two-photon uncaging of caged glutamate or application of 20 mM sucrose in rat hippocampal slice preparations. SV dispersion was reversible, persisted for 20-30 minutes, and was inhibited by MEK and ERK inhibitors and by expression of dominant-negative synapsin-I (dn-synapsin-I), in which ERK phosphorylation sites (sites 4, 5, 6) were mutated. Mechanical pressure directly activated ERK, as confirmed by a FRET-FLIM ERK probe in presynaptic terminals. Mechanical actions significantly reduced short-term depression (STD) by approximately 2-3 fold, as measured by glutamate release monitored via presynaptically expressed iGluSnFR combined with optogenetic stimulation, or by EPSCs recorded with whole-cell patch-clamp following electrical stimulation. Reduction in STD was prevented by MEK and ERK inhibitors and by dn-synapsin-I expression. These findings indicate that mechanical

pressure disperses SV clusters, thereby promoting vesicle mobilization through phosphorylation of MAPK phosphorylation sites on synapsin-I. Additionally, SNARE assembly, as measured by FRET-FLIM, showed that MEK inhibition selectively blocked the sustained phase of mechanically induced increases in SNARE assembly, suggesting reversible SNARE preassembly maintained by SV dispersion. We speculate that reduced STD is partially attributable to enhanced SNARE assembly resulting from vesicle dispersion-induced collisions (SV pressure), analogous to the immediate mechanical action-induced SNARE assembly enhancement observed under external pressure conditions.

Disclosures: F. Eto: None. H. Ucar: None. H. Okazaki: None. Y. Morimoto: None. H. Kasai: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.03/B27

Topic: B.04. Synaptic Transmission

Support: PID2019-105530GB-I00, PID2022-138957NBI00, FPU18/01700 funded by MICIU/AEI/10.13039/501100011033) and ERDF PY20-RE-053-USE, P18-FR-2144 funded by Junta de Andalucía-Consejería de Universidad, Investigación e Innovación and ERDF CIBERNED, ISCIII
Fundacion Tatiana Perez de Guzmán El Bueno

Title: Cysteine String Protein α (CSP α /DNAJC5) is essential for the maintenance of adult nervous system homeostasis

Authors: F. RUBIO-PASTOR¹, Á. MÁRQUEZ², S. LÓPEZ BEGINES^{1,3}, P. L. GARCIA-JUNCO¹, A. BHOJWANI-CABRERA², J. P. LOPEZ-ATALAYA², *R. FERNANDEZ-CHACON¹;

¹Inst. de Biomedicina de Sevilla IBiS-HUVR/CSIC/Univ. Sevilla & Dpt. Physiol. and Biophysics & CIBERNED, Seville, Spain; ²Inst. de Neurociencias, CSIC-UMH, Sant Joan d'Alacant, Spain; ³Luxembourg Ctr. for Systems Biomedicine (LCSB), Univ. Luxembourg, Belvaux, Luxembourg

Abstract: The continuous maintenance of synaptic proteins is fundamental for neuronal viability and function throughout life, yet the underlying molecular mechanisms remain incompletely understood. The co-chaperone Cysteine String Protein α (CSP α /DNAJC5) has been implicated in protecting synapses from degeneration, but its precise cellular and molecular roles are still being elucidated. Mutations in DNAJC5 cause adult-onset autosomal dominant neuronal ceroid lipofuscinosis (CLN4/Kufs disease), a devastating neurodegenerative disorder affecting young adults. Conventional CSP α /DNAJC5 knockout (KO) mice exhibit early lethality, limiting

the study of its function in the adult or aging brain in vivo. To overcome this limitation, we developed a tamoxifen-inducible conditional knockout mouse model (UBCCreERT2:Dnajc5^{flox/flox}) that allows temporal deletion of CSP α /DNAJC5 in adulthood. Acute loss of CSP α /DNAJC5 in these mice resulted in severe neurological decline and premature death, revealing its critical function in the mature nervous system. Importantly, this phenotype occurred without evidence of lipofuscin accumulation, confirming that CSP α /DNAJC5 deficiency does not mimic CLN4 pathology, as recently described (Lopez-Begines, Borjini et al., Science Advances, 2025). Unexpectedly, CSP α /DNAJC5 deletion also led to skin hyperpigmentation and keratinocyte abnormalities, suggesting a novel role in skin homeostasis. Transcriptomic profiling of cortical tissue revealed dysregulation in genes associated with lipid metabolism, synaptic integrity, glial-neuronal signalling, and myelination. Although systemic adeno-associated virus (AAV) delivery of CSP α /DNAJC5 using the PHP.eB capsid achieved widespread neuronal transduction, it failed to rescue the severe neurological phenotype. This suggests that once neuronal dysfunction is initiated, virally delivered CSP α /DNAJC5 may be insufficient to reverse the damage, possibly due to inadequate viral load. Our results demonstrate that CSP α /DNAJC5 is indispensable not only during postnatal development but also for sustaining neuronal function in the mature and aging adult brain. Furthermore, this study highlights novel molecular pathways potentially involved in CSP α /DNAJC5-related neurodegeneration.

Disclosures: F. Rubio-Pastor: None. Á. Márquez: None. P.L. Garcia-Junco: None. A. Bhojwani-Cabrera: None. J.P. Lopez-Atalaya: None. R. Fernandez-Chacon: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.04/B28

Topic: B.04. Synaptic Transmission

Support: DFG SCHO 820/9-1
ibehave

Title: Resolving the total protein distribution in the synapse

Authors: *P. NEMCOVA, M. GALKOV, S. SCHOCH, D. DIETRICH;
Inst. of Cell. Neurosciences II, Univ. Hosp. Bonn, Bonn, Germany

Abstract: The efficiency of neurotransmission relies on the intricate interplay of presynaptic proteins at a specialized membrane region known as the active zone. Although the interactions among these proteins remain incompletely understood, previous studies have shown that approximately 20 synaptic protein types form aligned clusters - trans-synaptic nanocolumns - spanning the pre- and postsynaptic compartments. However, this represents only a small fraction of the thousands of proteins present at synapses. Here, we investigate the distribution of total

synaptic proteins using 3D electron microscopy (FIB-SEM) combined with phosphotungstic acid (PTA) staining in murine brain slices. We improve the 3D electron microscopy by deconvolution of detected electrons which are backscattered from within the tissue. With this approach, we address three central questions:

1. What is the total protein distribution in the presynapse, postsynapse, and synaptic cleft? The synaptic cleft, in particular, has only been briefly explored in cultured cells, which have lower protein content in this region. Our reconstructions of the synaptic cleft in brain slices show that the majority of synapses contain dense cleft material, approximately 10 nm thick, with gaps of ~50 nm in diameter. 2. Is there trans-synaptic nanoalignment at the level of total protein content? Several specific protein types show alignment, but the total protein distribution does not show this phenomenon anymore. In addition, presynaptic clusters are anti-aligned with gaps in the synaptic cleft. 3. What is the molecular weight of a single presynaptic cluster? Biochemical purification does not currently allow analysis of individual protein clusters, such as presynaptic dense projections (~50 nm in diameter) or the postsynaptic compartment (~20 nm thick). Here, we establish a new method for measuring protein concentration from FIB-SEM data, using nuclear pore complexes and ribosomes as standards. We report that a single presynaptic dense projection has a mass of approximately 80 MDa, sufficient to host about 350 protein copies. Together, these findings challenge existing assumptions about synaptic organization, revealing a more heterogeneous and complex synaptic landscape than previously appreciated.

Disclosures: P. Nemcova: None. M. Galkov: None. S. Schoch: None. D. Dietrich: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.05/B29

Topic: B.04. Synaptic Transmission

Support: NIH Grant 5F31EY034776-02

Title: Dynamins regulate vesicle formation and synapse function in retinal rod bipolar cells but are not required for cell survival

Authors: *T. E. ZAPADKA¹, C. HANKE-GOGOKHIA², T. K. MAUGEL⁴, J. H. SINGER⁵, J. B. DEMB³;

¹Cell. and Mol. Physiol., ²Ophthalmology and Visual Sci., ³Ophthalmology & Visual Sci., Yale Univ., New Haven, CT; ⁴Univ. of Maryland, College Park, MD; ⁵Biol., Univ. of Maryland, Col. Park Neurosci. and Cognitive Sci. Program, College Park, MD

Abstract: Excitatory presynaptic active zones in both photoreceptors and bipolar cells in the retina contain ribbon structures that tether synaptic vesicles. Ribbon synapses are thought to support high rates of synaptic vesicle release via exocytosis, which is accompanied by vesicle retrieval, via endocytosis. Endocytosis involves the pinching off of newly formed vesicles, which

commonly requires the membrane scission protein dynamin (Dnm). Dnm1 and -3 are neuronal isoforms, and Dnm2 is ubiquitously expressed and apparently supports housekeeping functions. We showed that rod photoreceptors depend redundantly on Dnm1 and -3; their conditional deletion causes dysfunction and degeneration of rod synapses over 1-6 months (Hanke-Gogokhia et al., 2024). Here, we evaluated deletion of Dnm isoforms in rod bipolar cells using the BAC-Pcp2-IRES-Cre driver line. Dnm1 and 2 were conditionally deleted using floxed lines; Dnm3 was either conditionally or globally deleted. Rod bipolar cell synapses were evaluated by immunostaining with an antibody against Protein Kinase C, electroretinogram (ERG) measurements, and electron microscopy of axon terminals. Immunostaining of Dnm1/3 conditional knockout (cKO) rod bipolar cells did not show an obvious structural phenotype at postnatal day 60 (P60); whereas cKO of an additional Dnm2 allele (i.e., leaving a single copy of Dnm2 intact) resulted in swollen terminals, which persisted at P180. ERG b-wave amplitudes in 'Dnm2-1 copy' mice were normal at P60 but reduced at P180; whereas the a-wave was normal at both ages. Electron microscopy showed a low density of enlarged synaptic vesicles adjacent to ribbons in rod bipolar terminals at P180 in Dnm2-1 copy cells. Rod bipolar cells lacking all three dynamin isoforms (triple KO) could be immunostained at P180, suggesting their survival without Dnm expression. These results show that rod bipolar cells in mouse retina depend on Dnm for normal synapse structure and function, although there is apparently greater redundancy between Dnm isoforms, as compared to rods, with greater reliance on Dnm2. Further, rod bipolar cells apparently survive in the absence of dynamin expression, suggesting that housekeeping functions normally mediated by dynamin can be maintained by other mechanisms.

Disclosures: T.E. Zapadka: None. C. Hanke-Gogokhia: None. T.K. Maugel: None. J.H. Singer: None. J.B. Demb: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.06/B30

Topic: B.04. Synaptic Transmission

Support: PRIN2022-2022H4MHXE-CUP B53D23018620006 - Finanziamento dell'Unione Europea – NextGenerationEU – missione 4, componente 2, investimento 1.1.

Title: The HDAC4 dependent regulation of presynaptic function by SUMOylation is lost in the 3xTg mouse model of AD

Authors: *W. TOSCANELLI¹, A. BERTOZZI¹, G. ACETO¹, R. PIACENTINI¹, C. RIPOLI¹, B. CANNATA², M. D'ASCENZO¹, C. GRASSI¹, C. COLUSSI³;

¹Univ. Cattolica del Sacro Cuore, Rome, Italy; ²Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; ³Italian Natl. Res. Council, Rome, Italy

Abstract: Synaptic dysfunction appears early in Alzheimer's disease and worsens with cognitive decline. Despite a clear presynaptic involvement, its main causes remain unclear. Here, we investigated the role of the class II member HDAC4 as new regulator of presynaptic function in the 3xTg mouse model of AD by molecular and functional approaches and by using a cytoplasmic mutant form of HDAC4 (HDAC^{SD}) localized at synapses, focusing on its SUMOylation activity. By co-IP we found that the interaction of HDAC4 with synapsin I (synI) was reduced in hippocampal tissue of 3xTg mice compared with WT (fold decrease: 0.60 ± 0.07 AD vs WT) as a consequence of HDAC4 nuclear accumulation in AD. This was paralleled by a lower synI-SUMO2/3-ylation (fold decrease: 0.58 ± 0.07 AD vs WT), and by a lower formation of the complex synI/actin/synaptophysin in AD (fold decrease syn/actin 0.53 ± 0.02 AD vs WT; syn/syp 0.59 ± 0.14 AD vs WT). Overexpression of the cytoplasmic form of HDAC4^{SD} in AD hippocampal neurons recovered synI-SUMO2/3ylation and its clustering and interaction with actin favoring the formation of a reserve pool (fold change SUMO2/3-synI: WT, 1.00 ± 0.06 ; AD, 0.676 ± 0.08 ; AD-SD, 1.95 ± 0.56). Further we found that HDAC4^{SD} overexpression in AD neurons recovered the kinetic of synI phosphorylation (S9) after stimulation as well as the association with SVs and their release, analyzed by FM4-64, in comparison to GFP expressing AD neurons. Of note, the inhibition of SUMOylation through Anacardic Acid (AA) abrogated PS9-synI increase upon stimulation with KCl in AD neurons reversing the positive effect of HDAC4^{SD} expression (PS9-synI: AD^{SD} 1.00 ± 0.016 , AD^{SD}-KCl 1.66 ± 0.10 , AD^{SD}-AA 0.62 ± 0.09 , AD^{SD} KCl-AA 1.163 ± 0.15). Intra-hippocampal injection of the vector expressing HDAC4^{SD} in AD mice mitigated the oxidative and inflammatory AD phenotype (reduced levels of IBA-1, Nitro-tyrosine and A β expression) and ameliorated cognitive performance as evaluated by NOR and OPR. Our results suggest a new HDAC4 synaptic function based on SUMOylation, and its value as potential therapeutic tool to recover AD pathology.

Disclosures: W. Toscanelli: None. A. Bertozzi: None. G. Aceto: None. R. Piacentini: None. C. Ripoli: None. B. Cannata: None. M. D'Ascenzo: None. C. Grassi: None. C. Colussi: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.07/B31

Topic: B.04. Synaptic Transmission

Support: NINDS R01NS111978
The Farmer Family Foundation
Aligning Science Across Parkinson's [ASAP-020495] through the
Michael J. Fox Foundation for Parkinson's Research (MJFF)
Parkinson's Foundation Launch award PF-LAUNCH-1046253

Title: Context-dependent functions of alpha-synuclein at synapses revealed by gene editing

Authors: *L. A. PARRA-RIVAS¹, K. MADHIVANAN⁴, B. AULSTON², R. SHARMA³, A. T. NABB⁵, R. N. CABALLERO⁷, P. M. JENKINS⁸, C. LETERRIER⁹, F. A. MEUNIER¹⁰, S. ROY⁶;

¹Univ. of California San Diego, San Diego, CA; ²Univ. of California San Diego, La Jolla, CA; ³Pathology, Univ. of California San Diego, La Jolla, CA; ⁴Pathology, UCSD, La Jolla, CA; ⁵Pathology, UCSD, San Diego, CA; ⁶Departments of Pathology and Neurosciences, UCSD, La Jolla, CA; ⁷Pharmacol., Univ. of Michigan, Ann Arbor, MI; ⁸Dept. of Pharmacology, Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI; ⁹CRN2M, Marseille Cedex 15, France; ¹⁰The Univ. of Queensland, Brisbane, Australia

Abstract: Despite decades of study, the physiological function of α -synuclein (α -syn) remains poorly understood. Although α -syn knockout mice display only mild phenotypes, many prior investigations have relied on overexpression systems or triple synuclein knockouts, making it difficult to disentangle specific effects from compensatory mechanisms. To precisely define α -syn's synaptic role, we employed CRISPR-based gene editing in cultured mouse hippocampal neurons to selectively inactivate or activate α -syn, minimizing disruption to other synuclein family members. We performed an unbiased, multi-modal analysis combining synaptic vesicle (SV) recycling assays, electrophysiology, single-molecule tracking, super-resolution, TIRF microscopy, and electron microscopy (EM). Under basal conditions, α -syn depletion led to a significant increase in exocytosis and enhanced mobility of reserve pool SVs. In contrast, CRISPR-mediated activation of α -syn suppressed these parameters. Notably, phosphorylation at serine-129 promoted distal clustering of SVs, implicating α -syn in reserve pool organization. During sustained neuronal activity, however, α -syn loss selectively impaired endocytosis without altering exocytosis. Super-resolution and TIRF imaging revealed activity-dependent translocation of α -syn to peri-active zones, supporting a direct role in SV retrieval. At the ultrastructural level, EM revealed enlarged vesicles in α -syn-deficient neurons—a hallmark of endocytic defects. Consistent with this, stimulated neurons lacking α -syn exhibited significantly reduced FM dye uptake, further supporting its role in endocytosis. Complementary in vivo proximity labeling (BioID) combined with mass spectrometry identified an activity-dependent α -syn interactome enriched for endocytic proteins, reinforcing its functional engagement in SV retrieval during high neuronal activity. Together, these findings position α -syn as a dynamic regulator of synaptic vesicle recycling, with independent roles in exocytosis at rest and endocytosis during stimulation. This context-dependent functionality offers key insights into the physiological relevance of α -syn and its potential contributions to synaptic dysfunction in neurodegenerative disease.

Disclosures: L.A. Parra-Rivas: None. K. Madhivanan: None. B. Aulston: None. R. Sharma: None. A.T. Nabb: None. R.N. Caballero: None. P.M. Jenkins: None. C. Leterrier: None. F.A. Meunier: None. S. Roy: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.08/B32

Topic: B.04. Synaptic Transmission

Support: NSF Grant #: 2131750

Title: Differential overexpression of the vesicular acetylcholine transporter and its effects on organismal survival and locomotion during the lifespan in *Drosophila*

Authors: *K. ROSIKON¹, A. ATHEYBY², H. O. LAWAL³;

²Biol. Sci., ³Biol., ¹Delaware State Univ., Dover, DE

Abstract: Impairment in cholinergic neurotransmission is associated with normal and pathological aging, making cholinergic release a subject of sustained interest. The vesicular acetylcholine transporter (VACHT) is responsible for the packaging of ACh for exocytotic release. Although there is a plethora of knowledge about the molecular machinery that regulates ACh, the exact manner in which VACHT, an essential component of ACh regulation, alters ACh-linked neuronal function is not fully understood. Here, we use the overexpression of VACHT as a tool to increase the amount of ACh released into the synaptic cleft. Previously, we showed that vast increases in VACHT expression cause severe behavioral deficits, including a sharp decline in lifespan. Our current study is focused on testing the hypothesis that more moderate increases in VACHT expression will not only lead to less severe effects but also beneficial ones. To test this idea, we screened eight VACHT overexpressing lines with varying levels of increased expression. We report the intriguing results that while strong increases in VACHT produced a corresponding decrease in lifespan, a less drastic overexpression of the protein led to a less steep decline in lifespan. Moreover, our preliminary data indicate that VACHT overexpression caused an age-dependent decrease in locomotion ability in all lines tested. Further, immunohistochemical analysis showed that at least one VACHT overexpressor showed a strong increase in localization of the protein to punctae in cholinergic neurons of the optic lobe, indicative of increased presence in synaptic vesicles. Additionally, we used CRISPR-Cas9 to generate endogenously tag VACHT to enable to study real-time changes in protein localization in the fly brain. Taken together, these data indicate that morphological and behavioral effects of VACHT overexpression are driven by the levels of the protein's expression and inform further studies aimed at identifying precisely which dial in VACHT expression could lead to a beneficial effect on synaptic neurotransmission.

Disclosures: K. Rosikon: None. A. Atheby: None. H.O. Lawal: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.09/B33

Topic: B.04. Synaptic Transmission

Title: GABAB autoreceptors act via a G $\beta\gamma$ -SNARE complex interaction in mouse hippocampus

Authors: *I. LU¹, Z. ZURAWSKI¹, S. T. ALFORD²;

¹Anat. and Cell Biol., ²Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL

Abstract: In presynaptic terminals, membrane-delimited G_{i/o} GPCR-mediated presynaptic inhibition is ubiquitous and acts through G $\beta\gamma$ to inhibit Ca²⁺ entry, or directly at SNARE complexes to inhibit Ca²⁺-dependent synaptotagmin-SNARE complex interactions. At inhibitory interneuron presynaptic terminals that locally inhibit pyramidal neurons, inhibition is autoinhibited by GABA_B autoreceptors. The GABA_BR agonist baclofen inhibits output from inhibitory interneurons and is thought to act by inhibiting presynaptic Ca²⁺ channels, although the evidence is indirect. During repetitive stimulation of GABAergic neurons IPSCs late in the train are inhibited and this late inhibition is selectively reduced by GABA_BR antagonists. We investigated the mechanisms by which this fast autoinhibition acts. Inhibitory neurons in the hippocampal CA1 region were transfected with jGCaMP8f under the mDLX enhancer and imaged during stimulation to evoke a presynaptic Ca²⁺ transient imaged at the proximal dendrites and soma of pyramidal neurons. This transient was significantly inhibited by baclofen (1-10 μ M). However during repetitive stimulation (2-20Hz) sequential Ca²⁺ transients showed identical amplitudes and these responses were unaffected by the GABA_BR antagonist CGP55845 (1-10 μ M). We have developed a mutant mouse (SNAP25 Δ 3) that lacks the 3 C-terminal residues and shows markedly reduced G_{i/o} inhibition mediated by G $\beta\gamma$ -SNARE interactions. In this mouse, GABAergic neurotransmission was recorded either by whole cell patch clamp of CA1 pyramidal neurons or by measuring GABA release using iGABASnFR expressed in CA1 neurons, following local stimulation. Events evoked by repetitive stimulation show significantly less autoinhibition than in WT mice (WT fifth response reduced to 0.42 $\pm$ 0.04, SNAP25 Δ 3 to 0.75 $\pm$ 0.09 of first stimulus at 20Hz). Additionally antagonism of GABA_BRs using CGP showed significantly less enhancement of events late in the stimulus train. Taken together, our results demonstrate a striking difference between rapid activation of presynaptic GABA_BRs compared to slow activation by washin of an exogenous agonist. Rapid GABA_BR activation during stimulus trains recruits G $\beta\gamma$ at the SNARE complex. Slow activation by agonist (baclofen) application recruits a G_{i/o} GPCR activated mechanism that also inhibits presynaptic Ca²⁺ channels.

Disclosures: I. Lu: None. Z. Zurawski: None. S.T. Alford: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.10/Web Only

Topic: B.04. Synaptic Transmission

Title: Presynaptic CB2 Receptors in Cortico-Accumbal Terminals Regulate Glutamate Release and Are Dependent on Anterior Cingulate Cortex Integrity

Authors: ***I. O. CONDE ROJAS**¹, J. O. SUAREZ-ORTIZ², F. CORTÉS SALAZAR³, V. LÓPEZ-ALONSO⁴, J. MANCILLA-DIAZ⁵, G. B. FLORAN⁶, R. ESCARTIN-PEREZ⁷;

¹Univ. Nacional Autónoma de México, FES Iztacala., Ciudad de México, Mexico; ²Grupo de Investigación en Nutrición, Univ. Nacional Autónoma de México, Tlalnepantla de Baz, Mexico; ³Facultad de Estudios Superiores Iztacala, Univ. Nacional Autónoma de México, Facultad De Estudios Superiores Iztacala, Mexico; ⁴Facultad De Estudios Superiores Iztacala, Tlalnepantla, Mexico; ⁵Facultad De Estudios Superiores Iztacala, NAUCALPAN, Mexico; ⁶Physiology, Biophysics and Neurosciences, Ctr. de Investigación y de Estudios Avanzados del IPN, CDMX, Mexico; ⁷División de Investigación y Posgrado, UNAM, FES Iztacala, Tlalnepantla de Baz, Mexico

Abstract: The nucleus accumbens (NAc), a key region integrating inputs from the prefrontal cortex and limbic structures, plays a crucial role in reinforcement and natural reward-seeking behaviors. The endocannabinoid (eCB) system contributes to several central nervous system (CNS) functions, including executive processes such as decision making. Previous studies have shown that the NAc shell receives direct glutamatergic projections and that reduced eCB synthesis in GABAergic medium spiny neurons (MSNs) diminishes the pursuit of food and other natural rewards. However, the precise mechanisms underlying these effects remain poorly understood. Given the close relationship between glutamatergic neurotransmission in the NAc shell and reward processing, we investigated the role of cannabinoid receptor type 2 (CB2r) in this pathway using behavioral, neurochemical, and electrophysiological methods. Bath application of the selective CB2r agonist GW405833 (GW, 1 μ M) significantly reduced AMPA/NMDA mediated evoked excitatory postsynaptic currents (eEPSCs) in MSNs of the NAc shell. This inhibitory effect was prevented by the CB2-selective inverse agonist AM630 (100 nM), but not by CB1 receptor antagonism (AM281, 100 nM), indicating a CB2-specific mechanism. Further analysis revealed that GW reduced the amplitude of the first eEPSC and paired-pulse facilitation, consistent with a presynaptic mechanism of CB2r mediated inhibition. Additionally, the inhibitory effect of CB2r activation was blocked by selective inhibition of P/Q-type Ca^{2+} channels using ω -agatoxin-TK (200 nM) and Galleine (10 μ M), whereas inhibition of L- and N-type channels (1 μ M) had no effect. Finally, lesions induced with kainic acid in the anterior cingulate cortex led to decreased CB2r protein levels in accumbens synaptosomes, suggesting that a portion of CB2r in the NAc originates from this cortical region.

Disclosures: I.O. Conde Rojas: None. J.O. Suarez-Ortiz: None. F. Cortés Salazar: None. V. López-Alonso: None. J. Mancilla-Diaz: None. G.B. Floran: None. R. Escartin-Perez: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.11/B34

Topic: B.04. Synaptic Transmission

Support: DFG (DU313\6-3)

Title: Role of synaptotagmin 7 in regulating presynaptic function at the *Drosophila* neuromuscular junction

Authors: *J. ARIAN, S. HILGERT, C. DUCH;
Johannes Gutenberg Univ. of Mainz, Mainz, Germany

Abstract: Calcium signals contribute to several fundamental presynaptic functions, such as synaptic vesicle (SV) release, recycling, replenishment of the readily releasable pool (RRP) and synaptic plasticity. One way to coordinate these processes is to utilize calcium sensing proteins with different demands to the kinetics and amplitudes of the calcium signals like the family of synaptotagmin proteins. In mammalian synapses fast and low affinity synaptotagmins are known to ensure synchronous SV release, while the slower but higher affinity synaptotagmin 7 (Syt7) contributes to the regulation of short-term plasticity (STP), RRP replenishment and asynchronous release (AR) (Huson and Regehr, 2020). Although it has been suggested that many of the mammalian Syt7 functions may not be conserved in flies (Guan et al., 2020), we find considerable functional conservation for Syt7 at the *Drosophila* larval neuromuscular junction (NMJ). Here we show that Syt7 regulates SV replenishment, short-term facilitation and AR together with the voltage gated calcium channel (VGCC) Dmca1D (homolog to vertebrate Ca_v1) at the NMJ. First, Syt7 is required for the fast phase of readily releasable pool (RRP) recovery after high frequency stimulation induced depletion. Knockdown of Ca_v1 further speeds up fast RRP recovery, whereas knockdown of the plasma membrane bound calcium ATPase (PMCA) inhibits Syt7 mediated fast RRP replenishment, thus indicating that this function of Syt7 is inhibited by excess calcium. Given that calcium influx through Ca_v1 activation augments SV recycling rates (Krick et al., PNAS, 2021) and decreases fast RRP replenishment (this study) synaptic function can likely be maintained better during prolonged high frequency use, though at smaller transmission amplitudes. Second, short-term facilitation as observed upon Ca_v1 knock down is abolished upon concomitant Syt7 knock out, indicating that Syt7 is required for STP as reported for mammals. Third, Syt7 is required for AR. At the NMJ, AR is unmasked in basigin mutants and abolished by concomitant Syt7 knock out. Syt7 induced AR increases total charge transfer during high frequency activity, as also reported in mammals (Luo and Südhof, 2017). By contrast, a decrease in release probability is a fly-specific Syt7 function (Guan et al., 2020), and we currently address the hypothesis that this is caused by Syt7/Syt1 competition in the active zone. Apart from this, our data suggest that Syt7 contributes to the cooperative tuning and orchestration of short-term plasticity, RRP replenishment, and AR, as in mammals.

Disclosures: J. Arian: None. S. Hilgert: None. C. Duch: None.

Poster

PSTR006: Presynaptic Mechanisms, Organization, and Structure I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR006.12/B35

Topic: B.04. Synaptic Transmission

Title: Heterogeneous release probability and short-term plasticity at CA1 pyramidal cell output synapses revealed with iGluSNFR3 imaging of individual synapses in vitro

Authors: *N. E. HOLDERITH, F. BALINT, Z. NUSSER;
HUN-REN Inst. of Exptl. Med., Budapest, Hungary

Abstract: Postsynaptic target cell type-dependent variation in release probability and short-term plasticity (STP) at glutamatergic synapses enhance the computational power of cortical network. It is well-known that hippocampal CA1 pyramidal cells (CA1PCs) establish different synaptic connections on local GABAergic interneurons (INs), both in their efficacy and STP. However, the functional properties of synapses onto other CA1PCs remain elusive. Here we used iGluSNFR3 glutamate sensor imaging with 2-photon microscopy to measure glutamate release from single CA1PC boutons with identified postsynaptic targets. First, we verified iGluSNFR3's ability to reveal distinct glutamate release and STP at CA1PC - local IN synapses expressing the sensor postsynaptically either in oriens lacunosum-moleculare INs (O-LM INs, ChRNA2-Cre) or in parvalbumin expressing INs (PV INs, PV-Cre). Extracellular stimulation evoked iGluSNFR3 signals on O-LM IN dendrites showed characteristic short-term facilitation and a dramatic increase in response to phorbol dibutyrate (PDBU). The peak amplitudes of simultaneously measured evoked EPSCs and the iGluSNFR3 signals showed a linear correlation. Glutamate release from CA1PC boutons onto PV INs exhibited short-term depression (paired pulse ratio ~0.9), consistent with results obtained with whole-cell patch-clamp paired recordings. To reveal the properties of CA1 PC - CA1PC connections, iGluSNFR3 was expressed in CA1PCs allowing the measurement of glutamate release from a large number of boutons per cell (~25 boutons per CA1PCs). Our results reveal that at ~30% of the boutons no detectable iGluSNFR signal can be measured upon a complex high-frequency train of action potentials. Approximately 10% of boutons display depressing, whereas ~60% facilitating release properties upon 20Hz presynaptic activation. The peak amplitude of the 1st release was ~5 times larger of the depressing boutons, while no significant difference was found in the peak amplitude during an 80 Hz train after the 20 Hz preconditioning between the two STP bouton populations. Postsynaptic targets of the imaged boutons were identified using scanning electron microscopy. The majority of the identified targets (75%) were IN dendrites, while 25% were CA1PCs spines. IN targeting boutons displayed glutamate transients with variable STP patterns, and 16% were silent. Spine targeting boutons were silent for the 1st AP, and either remained silent for the whole train (25%) or showed short-term facilitation (75%). Our results demonstrate the usefulness of iGluSNFR3 for studying the output synapses of CA1PCs and revealed unique properties of CA1PC -PC connections.

Disclosures: N.E. Holderith: None. F. Balint: None. Z. Nusser: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.01/B36

Topic: H.04. Emotion

Support: NIH/NIBIB (P41-EB018783)
NIH/NIBIB (R01-EB026439)
NIH/NINDS (U24-NS109103)
NIH/NINDS (U01-NS108916)
NIH/NINDS (U01-NS128612)
NIH/NINDS (R21-NS128307)
NIH/NIMH (R01-MH120194)

Title: The relationship between ongoing oscillatory activity and saccade-related evoked potentials in humans

Authors: *G. TAN¹, P. DEMAREST¹, Y. LI¹, H. CHO¹, J. R. SWIFT², K. L. WAHLSTROM⁴, X. LIU¹, Z. LI¹, P. CETTINA¹, S. S. SIVAKUMAR¹, C. S. INMAN⁴, E. C. LEUTHARDT³, J. T. WILLIE³, P. BRUNNER³;

¹Washington Univ. in St. Louis, Saint Louis, MO; ³Neurosurg., ²Washington Univ. Sch. of Med., Saint Louis, MO; ⁴Psychology, Univ. of Utah, Salt Lake City, UT

Abstract: Saccade-related evoked potentials (EPs) were observed in both humans and non-human primates. Given the role of local field potentials in modulating local neuronal activity, saccade-related EPs were termed saccadic modulation, reflecting neural dynamics during visual exploration. We previously found that saccade-related EPs took two waveforms in humans, evidenced by a bimodal distribution of the intertrial correlation between local field potential following saccades. This raises a foundational question: What determines the polarity of saccade-related EPs? Answering this question is critical for understanding how the brain coordinates motor and sensory systems to optimize visual information processing. There are two competing theories on where the saccade-related EPs originate. Saccade-related EPs can be a corneal signal resulting from saccadic movement. Alternatively, saccade-related EPs may reflect the alignment of ongoing brain rhythms to saccades to support the temporal coordination of neural firing. Our previous findings lean towards the second hypothesis. To test this hypothesis, we investigated whether the polarity of saccade-locked EPs was determined by the phase of ongoing neural oscillations preceding saccades. We concurrently recorded intracranial EEG and gaze data in epilepsy patients implanted with depth electrodes while they performed a visual encoding task. We first identified the dominant frequency of ongoing oscillations per electrode by fitting a 1/f aperiodic model and detecting peaks in the residual spectrum. Instantaneous phase and power were extracted using the Hilbert transform applied to narrowband-filtered segments preceding saccade-related EPs. We found that trials with positive and negative EP polarity diverged progressively in phase as the time approached saccades. This phase separation exceeded surrogate null distributions generated by random permutations (Wilcoxon signed-rank test, $p < 0.001$). Rank-biserial effect sizes increased from 0.204 to 1.000 from 3 oscillation cycles before saccades to half an oscillation cycle before the onset of saccades. These findings suggest that saccadic modulation reflects the interaction between ongoing oscillation and saccadic eye movements.

Disclosures: G. Tan: None. P. Demarest: None. Y. Li: None. H. Cho: None. J.R. Swift: None. K.L. Wahlstrom: None. X. Liu: None. Z. Li: None. P. Cettina: None. S.S. Sivakumar: None. C.S. Inman: None. E.C. Leuthardt: None. J.T. Willie: None. P. Brunner: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.02/B37

Topic: B.07. Network Interactions

Support: NRC AiP Grant AiP-011

Title: Investigating blink-related oscillations during whole-body vibration: a pilot EEG study

Authors: *S. AZIZ^{1,3}, J. KEILLOR^{3,2}, R. DABKOWSKI³, A. B. SEKULER^{4,5}, S. WICKRAMASINGHE³, C. LIU⁶, E. ROUDAIA⁷, S. GHOSH HAJRA⁶, A. LAW^{3,2};
¹Cognitive Sci., ²Carleton Univ., Ottawa, ON, Canada; ³Natl. Res. Council, Ottawa, ON, Canada; ⁴Rotman Res. Inst., Baycrest Hlth. Sci., Toronto, ON, Canada; ⁵Univ. of Toronto, Toronto, ON, Canada; ⁶Florida Inst. of Technol., Melbourne, FL; ⁷Rotman Res. Inst., Montreal, QC, Canada

Abstract: Exposure to whole-body vibration (WBV) is a part of daily work for some, and may affect sensorimotor co-ordination and cognition (Shantakumar & Ahmed, 2023). The neural mechanisms underlying such effects are not well understood. Blink-Related Oscillations (BROs) are emerging as a novel neurophysiological signature of cognitive and sensorimotor processes that may be captured without interfering with task performance (Liu et al., 2020; Hajra et al., 2021). This pilot study explored the effects of task demand and WBV on blink rate (BR) and BROs during target tracking. Eight participants (35.8 ± 12.3 years, 3 female) completed two tracking tasks with and without WBV. Vertical WBV was delivered via the NRC's human-rated shaker simulating Bell 412 helicopter cockpit levels. The Multi-Attribute Task Battery (Miller et al., 2014) tracking subtask presented a moving target to participants. For active tracking, participants used a joystick to reposition the target back to center; for passive tracking, they mentally counted threshold crossings of the target. Electroencephalography (EEG) data were recorded with a 16-channel g.Nautilus system, and blinks were detected from forehead electrodes. Data was preprocessed using standard methods, including ICA to remove artifacts. Delta-band (0.5 - 4 Hz) blink-related oscillations were derived from POz, O1, and O2 electrodes. Preliminary results showed that BR was significantly modulated by task demands (active vs passive tracking) but not vibration exposure. Task performance was also not affected by vibration exposure. Blink rates were low during active tracking (no WBV: 7.8 ± 7.3 per minute; WBV: 7.4 ± 7.4) but increased during passive tracking (no WBV: 17.2 ± 12.8 ; WBV: 16.4 ± 9.7). In both cases, blinks generally occurred during quiescent periods in target motion when attentional demands were lower. Neurophysiological results revealed distinct task- and vibration-dependent changes in delta-band BRO morphology at different time periods following a blink. Specifically, WBV modulated the early blink-related potential (~100 ms post-blink; more negative with WBV), whereas task effects were observed ~550 ms post-blink (more positive with passive tracking). These findings suggest that BROs are sensitive not only to cognitive task

demands and sensory environment changes as previously reported, but also to the physical environmental context - an effect not previously reported. These findings provide preliminary evidence that BROs may serve as useful markers for brain adaptation to stressors like WBV. Larger studies are needed to further establish BROs as an index of cognitive engagement and sensorimotor integration.

Disclosures: S. Aziz: None. J. Keillor: None. R. Dabkowski: None. A.B. Sekuler: None. S. Wickramasinghe: None. C. Liu: None. E. Roudaia: None. S. Ghosh Hajra: None. A. Law: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.03/B38

Topic: I.10. Human Learning and Cognition

Title: Differential Effects of Musical Genres on Brain Wave Changes and Mood Dynamics: An EEG and Behavioral Analysis

Authors: *T. KHACHATRYAN¹, A. HOVHANNISYAN², H. KULHANDJIAN^{3,4};
¹Biol., California State University, Fresno, Fresno, CA; ²Biol., California State Univ. of Fresno, Fresno, CA; ³Electrical and Computer Engin., California State Univ. - Fresno, Fresno, CA; ⁴Electrical and Computer Engin., California State University-Fresno, Fresno, CA

Abstract: Music is a powerful stimulus capable of influencing both cognitive and emotional states, yet the neural mechanisms linking genre-specific auditory input with mood regulation remain underexplored. In this study, we examined how four musical genres—rock, jazz, classical, and ambient—affect emotional valence and brain wave activity, using electroencephalography (EEG) to measure neural responses and pre/post surveys to assess mood dynamics. Four participants each underwent two listening trials. During each trial, participants were blindfolded and exposed to two-minute excerpts of each genre, separated by 30-second baselines. EEG recordings using the OpenBCI Ganglion system captured activity across alpha (7.5-13 Hz), beta (13-30 Hz), theta (4-8 Hz), and delta (1.5-4 Hz) frequency bands. Data were analyzed in MATLAB and paired with behavioral self-reports. Our findings demonstrate that musical genres produce distinct effects on both brain wave patterns and emotional outcomes. Rock and jazz—fast-tempo genres—were associated with elevated alpha and beta waves, consistent with increased arousal, engagement, and prefrontal cortex activation. Rock music was found to be correlated to heightened anxiety and irritability. Classical and ambient music increased theta and delta wave activity, correlating with states of calmness, focus, and introspection. Jazz uniquely enhanced positive mood without elevating tension, suggesting a balanced affective profile. These results reinforce the role of music as a form of cognitive-emotional feedback, with genre-specific neural correlates observable through EEG. This study

offers insights into how music can act as both a cognitive reinforcer and an emotional regulator. Our findings have implications for affective neuroscience, music therapy, and non-pharmacological mood modulation.

Disclosures: T. Khachatryan: None. A. Hovhannisyan: None. H. Kulhandjian: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.04/B39

Topic: B.07. Network Interactions

Title: Subtle Geomagnetic Stimuli Modulate Resting-State Neural Oscillations in Global Networks

Authors: *C. D. K. CHEZZI, S. J. LEVAC, K. S. BRANIGAN, B. T. DOTTA;
Laurentian Univ., Sudbury, ON, Canada

Abstract: The influence of weak environmental stimuli on neural systems remains an underexplored frontier in Neuroscience. This study investigated whether subtle, naturally occurring and simulated geomagnetic fluctuations modulate large-scale neural dynamics in the absence of overt behavioural tasks. Across two experimental phases, we investigated the influence of geomagnetic activity on resting-state electroencephalographic (EEG) signals, with a focus on alpha (7-13 Hz) and theta (4-7 Hz) oscillations, both of which are key components of intrinsic neural activity. In Experiment 1, archival EEG data from 238 sessions, recorded under controlled eyes-closed, resting conditions, were analyzed in relation to daily Kp index values, a global measure of geomagnetic disturbance. Time-lagged correlational analyses revealed significant positive correlations between elevated geomagnetic activity and increased alpha and theta band power, particularly 20 days before EEG recordings. These effects were distributed across frontal, central, and caudal cortical regions, suggesting that even imperceptible environmental fluctuations may modulate widespread neural activity. In Experiment 2, 22 participants were exposed to simulated geomagnetic fields while seated at rest in an electromagnetically shielded environment. EEG recordings taken pre-exposure were compared to those taken 19 days post-exposure, revealing significant increases in alpha and theta power in right frontal and parietal regions [e.g., high alpha: $t(21)=3.253$, $p=.004$]. An intensity-dependent suppression of frontal theta power was also observed ($t(21)=2.945$, $p=0.008$). These findings provide evidence that subtle, non-sensory environmental inputs such as geomagnetic fluctuations can shape global cortical network activity without requiring behavioural engagement. The consistent right-hemispheric effects and delayed modulation patterns suggest that background electromagnetic stimuli may influence integrative and affective neural circuits at rest. This work supports a broader view of brain-environment interactions and highlights the importance of incorporating planetary-scale physical variables in models of human brain function.

Disclosures: C.D.K. Chezzi: None. S.J. Levac: None. K.S. Branigan: None. B.T. Dotta: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.05/B40

Topic: B.07. Network Interactions

Title: Signal Complexity as a Multi-Scale Marker of Neuronal Integrity: From EEG to Emerging Network-Level Data

Authors: *S. J. LEVAC, K. GHASSEMKHANI, B. T. DOTTA;
Laurentian Univ., Sudbury, ON, Canada

Abstract: Complex temporal dynamics are essential for functional neuronal networks, with signal complexity serving as a marker of adaptive neural communication. Reductions in neural signal complexity have been linked to cognitive decline, aging, and neurodegenerative diseases. One technique that has pushed this boundary is detrended fluctuation analysis (DFA), which assesses fractal complexity of any time series data, making it an efficient application for various measurement types. DFA thus offers a powerful approach for detecting functional degradation within neural systems. We applied DFA to electroencephalogram (EEG) recordings to assess long-range temporal correlations (LRTCs) in individuals with Alzheimer's disease (AD) compared to age-matched controls. Data was acquired from the OpenNeuro EEG database, we used recordings uploaded to the database by Miltiadous et al. (2023). AD patients exhibited significantly reduced LRTCs, with lower DFA exponents in the alpha band across both rostral ($p=0.0127$) and caudal ($p=0.0012$) regions, indicating disrupted large-scale temporal organization of neural activity. Complementary analysis revealed rostrocaudal asymmetries in fractal dimension, consistent with emerging evidence that AD selectively degrades network-level complexity and hierarchical integration. To explore whether signal complexity loss reflects a fundamental cellular stress response potentially contributing to neural dysfunction, we analyzed biophoton emission (a marker of oxidative and metabolic stress) in established cancer and non-cancerous cell models. We found that cancerous cells exhibit significantly reduced signal complexity of biophoton emissions compared to non-cancerous controls [$t(234)=1.893$, $p=0.03$]. Together, these data provide evidence that signal complexity loss is a unifying feature of pathological states across cellular and neural systems. We hypothesize that signal complexity loss observed in both biophoton and EEG data will also manifest at the level of neuronal network activity, as measured using multielectrode arrays (MEA). Parallel MEA experiments are underway to validate whether neuronal network activity mirrors the observed complexity loss at cellular and EEG levels. This work supports the development of unified biomarkers for assessing neuronal integrity and dysfunction across cellular, network, and systems levels.

Disclosures: S.J. Levac: None. K. Ghassemkhani: None. B.T. Dotta: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.06/B41

Topic: B.07. Network Interactions

Title: Reduced EEG Microstate Temporal Stability and Increased Entropy in the Resting State of Major Depressive Disorder

Authors: *K. GHASSEMKHANI¹, V. HOSSACK², B. T. DOTTA¹;

¹Sch. of Natural Sci., Laurentian Univ., Sudbury, ON, Canada; ²Wilfrid Laurier University, Waterloo, ON, Canada

Abstract: Given the growing prevalence of Major Depressive Disorder (MDD), electroencephalography (EEG) has the potential to highlight differences at small time scales between MDD and controls (HC). Microstates are transient (approximately 60-120 ms) global field power patterns which can reflect network dynamics, and their temporal dynamics have potential for highlighting different conditions. Multiscale entropy (MSE) is a measure of signal irregularity across various time scales. Dataset 1 was an open dataset of resting state recordings (N=57, 29 MDD, age and gender matched) compiled by Mumtaz (2016) [1], dataset 2 consisted of human EEG recordings from our lab paired with Millon Clinical Multiaxial Inventory (MCMI) data in non-clinical populations (N=59), both of which utilize 19 channels with the 10-20 system. The sampling rates for the first and second datasets are 256 Hz and 250 Hz, with a bandwidth of 1.5-30 Hz and 1.6-45 Hz, respectively. Artifact removal was done using common average reference and independent components analysis for eye and muscle artifacts. Sex differences were not assessed. The bandwidth for microstate computation was 2-20 Hz as is standard with microstate analysis of resting state data. For dataset 1, MDD displayed a significantly higher rate of microstate occurrences irrespective of class ($p=0.0006$), with the FDR correction (Benjamini and Hochberg method), significantly higher occurrences were observed in canonical microstates A ($p=0.0077$), B ($p=0.0232$), and C ($p=0.0038$) compared to HC. MDD patients showed significantly lower durations irrespective of class ($p=0.0006$) and in the individual classes B ($p=0.004$) and D ($p=0.0061$). MDD patients also displayed significantly higher short-scale sample entropy (average of scales 1-6) but not long (7-12) when comparing the 19-channel averages ($p<0.0001$). For dataset 2, we used MCMI Depression Base Rate (DBR) scores for this analysis. Spearman revealed a significant positive correlation when observing the 19-channel average for long-scale entropy and DBR scores ($\rho=0.375$, $p=0.009$). The results from dataset 1 and 2 indicate that signal entropy is not only effective in highlighting differences between HC and MDD as observed in dataset 1, but that these differences are also scalable as seen with DBR correlations with MSE values in dataset 2. EEG is a cost-effective tool with clinical potential for assessing MDD given the variety of analysis techniques

[1] Mumtaz, W. (2016). MDD Patients and Healthy Controls EEG Data (New) [Dataset]. Figshare. <https://doi.org/10.6084/m9.figshare.4244171.v2>

Disclosures: K. Ghassemkhani: None. V. Hossack: None. B.T. Dotta: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.07/B42

Topic: B.07. Network Interactions

Support: JST, PRESTO Grant Number JPMJPR23I1

Title: Event-related desynchronization is shaped by the interaction of periodic and aperiodic components in the human sensorimotor cortex

Authors: *S. IWAMA;

Dept. of Biosci. and Informatics, Fac. of Sci. and Technol., Keio Univ., Yokohama, Japan

Abstract: Recent empirical and theoretical demonstrations of population-level neural activity indicate that analysis of broadband and frequency-specific components effectively reveals the ongoing neural dynamics that mediate behavior. These studies suggest that local excitatory-inhibitory balance contributes to changes in broadband, 1/f-shaped aperiodic activity, while oscillatory activity found in a specific frequency is formed by shared neural populations in local regions. However, it remains unclear whether task-related neuronal desynchronization, known as event-related desynchronization (ERD), independently modulates both periodic and aperiodic neural activities, or whether these components interact in a coordinated manner. To characterize this, the author investigated the spatiotemporal characteristics of ERD during a variety of motor tasks, including motor preparation and motor imagery, as derived from scalp electroencephalograms (EEG), electrocorticography (ECoG), and magnetoencephalography (MEG) using previously acquired, multiple open datasets. We analyzed high-density EEG datasets (Iwama et al., 2023), MEG data from the Human Connectome Project (Larson-Prior et al., 2013), and ECoG data from Miller et al., 2019. The power spectral density (PSD) during motor tasks, extracted from regions of interest. Specifically, PSD from sensors over the contralateral sensorimotor cortex was calculated by short-term Fourier transform and sorted by their peak height at individual alpha frequency (IAF) after spectral detrending using specparam. The sorted PSD samples were averaged in 25th percentile intervals, and the four averaged samples were again subjected to specparam. We found a significant within-participant correlation between the IAF peak and aperiodic exponents across the three datasets (repeated-measures correlation, $r_m = 0.378 \pm 0.14$, all $p < 0.05$). Time-resolved analysis of modulation in the 1/f component indicated that overall ERD exceeding 15% led to significant modulation of the 1/f aperiodic exponent (paired t-test, $p < 0.05$). Collectively, these analyses extend the current

understanding of the interaction between high-frequency gamma-band activity and low-frequency alpha-band activity, framed in terms of periodic and aperiodic components in population-level activity.

Disclosures: S. Iwama: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.08/B43

Topic: B.07. Network Interactions

Title: Aperiodic activity as an EEG biomarker for sertraline response: Applications and limitations

Authors: *I. N. VAIRAGARE¹, S. E. SMITH^{2,3}, A. CHAPMAN^{8,4}, B. VOYTEK^{5,3,6,7};
¹Cognitive Sci., Univ. of California San Diego, La Jolla, CA; ²Wu Tsai Inst., Yale Univ., New Haven, CT; ³Neurosciences Grad. Program, ⁴Psychology, ⁵Cognitive Sci., ⁶Halıcıoğlu Data Sci. Inst., ⁷Kavli Inst. for Brain and Mind, UCSD, La Jolla, CA; ⁸Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Major Depressive Disorder (MDD) is an extremely common mood disorder, affecting an estimated 1 in 12 adults in the United States. It is typically treated with medications that target the brain's neuromodulatory systems, including selective serotonin reuptake inhibitors like sertraline. However, patient responses to sertraline and other psychiatric medications are variable, necessitating the development of biological indicators to guide treatment. These indicators range in purpose as signatures of MDD severity, predictive indicators of response to medication, and mechanistic indicators of therapeutic changes with treatment. The electroencephalogram (EEG) is an affordable and promising source of such indicators, but attempts to identify EEG indicators in MDD have been mostly inconclusive. Most EEG studies concentrate on predefined oscillatory frequency bands, overlooking the aperiodic component of neural activity, which manifests as a broadband 1/f-like trend in the EEG power spectrum. The aperiodic exponent, defined as the negative slope of the log-log spectrum, provides insight into the non-oscillatory background activity of the brain. Despite its relevance in other treatments for depression like ECT, aperiodic activity has not yet been examined in the context of antidepressant response to sertraline. Here, we test the hypothesis that the aperiodic exponent may serve as a biological indicator in MDD patients receiving sertraline treatment. We acquired a dataset of resting-state EEG (n = 272) from patients participating in a clinical trial of sertraline, the EMBARC study. In this analysis, we examined the utility of aperiodic and periodic spectral EEG components as 1) biological indicators of MDD severity, 2) as predictive indicators of sertraline treatment response, and 3) as mechanistic indicators of neural changes due to sertraline. Although the outcome of diagnostic and predictive analyses were inconclusive, we

identified a highly significant reduction in aperiodic exponent in patients who received sertraline, a change not observed in patients who received placebo. Analyses relating this observed change in exponent to therapeutic outcome is ongoing. By focusing on the aperiodic exponent, a parameter rarely emphasized in standard neurophysiological analyses, our findings explore its potential utility (or lack thereof) as a predictive biomarker and mechanistic indicator of treatment efficacy. This work provides a foundation for broader application of aperiodic spectral measures for other depression treatments and clinical populations.

Disclosures: I.N. Vairagare: None. S.E. Smith: None. A. Chapman: None. B. Voytek: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.09/B44

Topic: B.07. Network Interactions

Support: NSF GRFP (to DC)

Title: Timescale changes across typical neurodevelopment and ADHD

Authors: *D. CELLIER¹, O. DANCE², B. VOYTEK²;

¹UCSD, La Jolla, CA; ²Cognitive Sci., Univ. Of California, San Diego, La Jolla, CA

Abstract: Neural timescales capture the stochasticity or relative stability of a neural signal over time, and are thought to reflect the brain's integration of external and internal stimuli. Though neural timescales have been extensively studied in non-human primates, rodents, and adult humans, research on the trajectory of neural timescales across human development is sparse. Existing literature on aperiodic and oscillatory activity supports a strong hypothesis regarding developmental timescale changes: dominant oscillatory frequencies overall get stronger and the aperiodic signal flattens with age. These effects collectively suggest that the ratio of higher-to-lower frequency neural activity increases with age. We therefore predict that neural timescales decrease over development, and that this decrease in timescales will correspond to changes in the aperiodic exponent and oscillatory peak frequencies with age.

Our investigation uses a cross-sectional dataset of eyes-open and eyes-closed resting state EEG data from the Child Mind Institute of participants aged 5-21 years old. We extract from resting state EEG data several neural features: peak frequency and power of oscillatory activity, the slope and offset of the aperiodic signal, and neural timescales measured by the decay rate of the autocorrelation function (ACF). In a preliminary analysis of 238 participants aged 6-21, we observed a decrease in neural timescales with increasing age.

We additionally conducted an exploratory analysis of neural timescales in ADHD (n = 103).

Prior research has shown that children with ADHD have an increased ratio of theta-to-beta oscillatory power, with mixed results showing both steeper and flatter aperiodic power spectra,

when compared to typically developing peers. We found that the neural timescales also decreased with age in children with ADHD, but we did not find that they significantly differed from age-matched controls.

Our results highlight the ACF as a powerful metric for understanding timescale changes in neurodevelopment, providing new insights into the relationship between neural activity and behavior across development.

Disclosures: D. Cellier: None. O. Dance: None. B. Voytek: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.10/B45

Topic: B.07. Network Interactions

Support: Whitehall Foundation Grant 2017-12-73
National Institute of Mental Health (R00MH126161)

Title: The Effect of Electrical Transcranial Random Aperiodic Stimulation on Working Memory

Authors: *Q. VAN ENGEN¹, B. VOYTEK², J. RIDDLE³;

¹UCSD, San diego, CA; ²Cognitive Sci., Univ. Of California, San Diego, La Jolla, CA;

³Psychology, Florida State Univ., Tallahassee, FL

Abstract: Working memory (WM) is a core cognitive function that actively maintains information in mind. It is limited by its storage capacity. Much research has investigated the underlying mechanisms of WM, focussing mainly on oscillatory dynamics that arise from synchronous neural activity. However, most neuronal activity manifests as asynchronous, aperiodic activity, often considered “background activity” or noise. Also described as 1/f, power-law or broadband activity, aperiodic activity manifests as unstructured fluctuations in an EEG signal, with higher power in the low-frequency range, and lower power in the high-frequency range. Recent work demonstrates that aperiodic activity dynamically flattens (lower exponent), during the delay period of visual WM tasks, theorized to reflect tonic excitatory drive. Furthermore, WM load increases are associated with more flattening as well. For this reason, investigating aperiodic activity in relation to WM is especially interesting, given that computational models of WM also stress the importance of an excitation/inhibition balanced network. Here, we have created a new non-invasive neurostimulation protocol to test this relationship between aperiodic slope and WM causally: transcranial Random Aperiodic Stimulation (tRAS). Using a randomized, double-blind, placebo-controlled, crossover neurostimulation protocol, we target endogenous aperiodic activity in order to test its functional role in human visual WM. Participants came to the lab for two sessions where they performed a delayed continuous report visual WM task to test their WM capacity and precision. The first

session served as a baseline measure in which no stimulation was applied, and individual WM capacity was captured. Coming back to session 2, individualized high versus low WM loads were used in combination with three stimulus conditions to manipulate the aperiodic slope: steep-tRAS, flat-tRAS, and sham. Data analysis is still ongoing. Initial results show that in session 1, we did not replicate initial findings of a flatter aperiodic slope with an increase in WM load, even though participants showed higher errors on the higher loads. In session 2, we capture behavioral performance with the Zhang & Luck (2004) model. We see a trending interaction effect of the guess rates between stimulation type and WM loads. While the data are currently still under investigation, we believe our work aids in our understanding of the underlying electrophysiological mechanisms of visual WM.

Disclosures: Q. van Engen: None. B. Voytek: None. J. Riddle: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.11/B46

Topic: B.07. Network Interactions

Title: Beyond All-or-Nothing: Action Potentials Dynamically Vary with Stimulation and Network State

Authors: *B. MARTIN-BURGOS¹, P. D. RIVIERE³, R. HAMMONDS⁴, A. L. JUAVINETT², B. VOYTEK⁵;

²Biol. Sci., ¹UC San Diego, San Diego, CA; ³Cognitive Sci., ⁴Halicioglu Data Sci. Inst., Univ. of California San Diego, La Jolla, CA; ⁵Cognitive Sci., Univ. Of California, San Diego, La Jolla, CA

Abstract: Individual neurons' action potentials (APs) have a dynamic waveform, the shape of which differs by neuron subtype and species. In analyses of single-unit data, however, this waveform is reduced to a binary "all-or-nothing" event after spike sorting, with systems and cognitive neuroscience focusing on the number and timing of spike events. This analytical convenience has resulted in theories of neural coding that assume binarity: rate, temporal, phase, and population coding all assume binary spiking. Despite this assumption, a growing body of evidence shows that AP waveforms exhibit systematic, within-neuron variation that may carry information beyond the rate or timing of discharge and is often ignored.

To examine whether spike-to-spike variability is stochastic or informative, we developed an AP parameterization approach that quantifies fine-scale features of intracellular spike waveforms. Using this parameterization on patch-clamp recordings of APs, we find within-neuron correlations between features such that, for example, individual APs that decay faster result in subsequent spikes occurring more quickly.

To study how AP waveform varies with both stimulus and network state, we applied this

approach to two datasets. First, we analyzed a patch-clamp dataset with current injection protocols (constant, ramp, pink noise). We found that stimulation type systematically influenced AP waveform, and that features of the pink noise stimulus (amplitude, variance) correlated with the shape of APs. Next, we analyzed a dataset of simultaneously recorded patch-clamp APs and local-field potentials (LFPs) in rats. This allowed us to examine, for the first time, the causal influence of the LFP on AP shape. We observed within-neuron differences in spike waveform features related to LFP aperiodic activity and gamma oscillatory states that have been overlooked by traditional analyses. These findings provide preliminary evidence for the importance of studying within-neuron variability in AP waveform alongside traditional spiking metrics to deepen our understanding of neural coding and cognition. They also carry significant potential implications for the inference of single-unit identity using spike sorting algorithms, which often assume within-neuron waveform stability.

Disclosures: **B. Martin-Burgos:** None. **P.D. Riviere:** None. **R. Hammonds:** None. **A.L. Juavinett:** None. **B. Voytek:** None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.12/B47

Topic: B.07. Network Interactions

Support: Burroughs Welcome Fund
NIH/NIGMS IRACDA K12 GM068524
NIH/NIMH Blueprint D-SPAN Award K00 MH132569

Title: Disrupted aperiodic neural activity signatures in Rett syndrome across human EEG and Mecp2 mouse model electrophysiology

Authors: ***C. CAZARES**¹, **S. METANAT**¹, **K. LYON**², **N. GANDY**¹, **D. KRANZ**^{3,4}, **A. R. LEVIN**³, **M. FAGIOLINI**^{3,4}, **C. A. NELSON**^{4,3}, **B. VOYTEK**^{1,5};

¹Cognitive Sci., UCSD, San Diego, CA; ²Mol. Neurobio., Salk Inst. for Biol. Studies, San Diego, CA; ³Boston Children's Hosp., Brookline, MA; ⁴Harvard Univ., Cambridge, MA; ⁵Halıcıoğlu Data Sci. Inst., San Diego, CA

Abstract: Rett syndrome, caused by mutations in the X-linked Mecp2 gene, is characterized by typical early development followed by developmental regression around 18 months of age, leading to severe cognitive and motor dysfunction. While abnormalities of oscillatory neural activity have been reported in Rett syndrome patient EEG, aperiodic neural activity patterns remain poorly understood, despite their emerging role as biomarkers of cortical dysfunction in neurodevelopmental conditions. One such marker is the aperiodic exponent, which reflects the slope of the 1/f power spectrum decay and is thought to serve as an index of cortical excitation-

inhibition balance. In typical development, the aperiodic exponent diminishes with age, leading to spectral “flattening”, which has been attributed to developmental changes in inhibitory drive. However, little is known about whether aperiodic measures differ in Rett syndrome compared to age-matched neurotypical children, if they can serve as markers of developmental divergence, or if these alterations can be recapitulated in widely used mouse models of the condition. Here, we analyzed task-free EEG data from 99 participants (61 girls with Rett syndrome in active regression and post-regression stages and 38 neurotypical controls, aged 2-14 years) alongside task-free, intracranial recordings from primary visual cortex in female *Mecp2*^{-/+} mice and littermate controls (2 per group, aged 14 weeks). Using spectral parameterization methods, we found that girls with Rett syndrome exhibited elevated aperiodic exponents compared to neurotypical controls, indicating “steeper” spectral slopes that contrast with the neurotypical “flattening” developmental trajectories reported in the literature. Complementary findings from *Mecp2*^{-/+} mice also revealed elevated aperiodic exponents relative to wild-type littermates, suggesting conserved alterations in aperiodic neural activity across species with consistent directional changes. These cross-species patterns suggest that *Mecp2* dysfunction fundamentally disrupts electrophysiological measures of cortical excitation-inhibition balance, potentially reflecting altered inhibitory function that contrasts with typical age-related decline in inhibitory drive. Our findings support the inclusion of task-free aperiodic neural activity measures as candidate biomarkers of neurodivergence in Rett syndrome that could provide objective assessments of therapeutic efficacy in clinical settings and accelerate treatment discovery in associated mouse models.

Disclosures: C. Cazares: None. S. Metanat: None. K. Lyon: None. N. Gandy: None. D. Kranz: None. A.R. Levin: None. M. Fagiolini: None. C.A. Nelson: None. B. Voytek: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.13/B48

Topic: B.07. Network Interactions

Support: UC HSI DDI Grant
NIH/NIMH Blueprint D-SPAN Award (K00 MH132569)
NIH/NIGMS IRACDA Award (K12 GM068524)

Title: Developmental trajectory of rhythmic and non-rhythmic spiking in hiPSC-derived cortical tissue

Authors: *A. HUTTON¹, D. PRE², A. T. WOOTEN², A. G. BANG², B. VOYTEK¹, C. CAZARES¹;

¹Cognitive Sci., Univ. of California San Diego, La Jolla, CA; ²Conrad Prebys Ctr. for Chem. Genomics, Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Coordinated neuronal activity is a characteristic and emergent feature in brain recordings. Human induced pluripotent stem cell (hiPSC) cultures offer a promising platform to identify the molecular and neural circuit origins of coordinated activity patterns, with unprecedented spatiotemporal resolution in human neural tissue, during pre-birth stages that are otherwise difficult to study during fetal cortex development. A growing body of work using human brain recordings has identified traveling waves, which are spatiotemporally organized patterns of neural activity, as one possible mechanism through which distant or distributed brain regions coordinate computational processes to facilitate cognition. However, it remains unclear how such structured dynamics emerge during early development and whether they can be modeled in simplified yet biologically representative, human-derived in vitro systems. In this study, we used hiPSC-derived cortical cultures expressing GABAergic, glutamatergic, and astrocytic molecular markers to investigate the spatiotemporal developmental trajectory of spontaneous and synchronized network activity. Cultures (n = 1,446) were plated and grown on microelectrode arrays (MEAs) to record spiking activity within ~300-second windows throughout 2 to 11 weeks post-plating. Preliminary analyses revealed a progressive increase in both spiking and bursting frequency during the first 7 weeks of development. Notably, individual cultures diverged into one of two distinct developmental profiles: either increasing burst frequency or increasing burst duration over time. These early trends suggest heterogeneous but organized modes of network maturation and provide a foundation for investigating the emergence of more structured dynamics. Ongoing analyses aim to quantify oscillatory (periodic) and broadband (aperiodic) spectral features, as well as the spatial propagation of these features, to characterize how and when traveling waves and other meso-scale activity patterns emerge in the development of hiPSC cortical cultures. This work introduces a high-throughput, tractable system for studying the developmental basis of neural circuit organization that can be leveraged to understand divergence from neurotypical development in cultures derived from patients affected by neurodevelopmental disorders.

Disclosures: A. Hutton: None. D. Pre: None. A.T. Wooten: None. A.G. Bang: None. B. Voytek: None. C. Cazares: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.14/B49

Topic: B.07. Network Interactions

Support: FAPESP Grant 2018/12605-8
FAPESP Grant 2024/15729-0

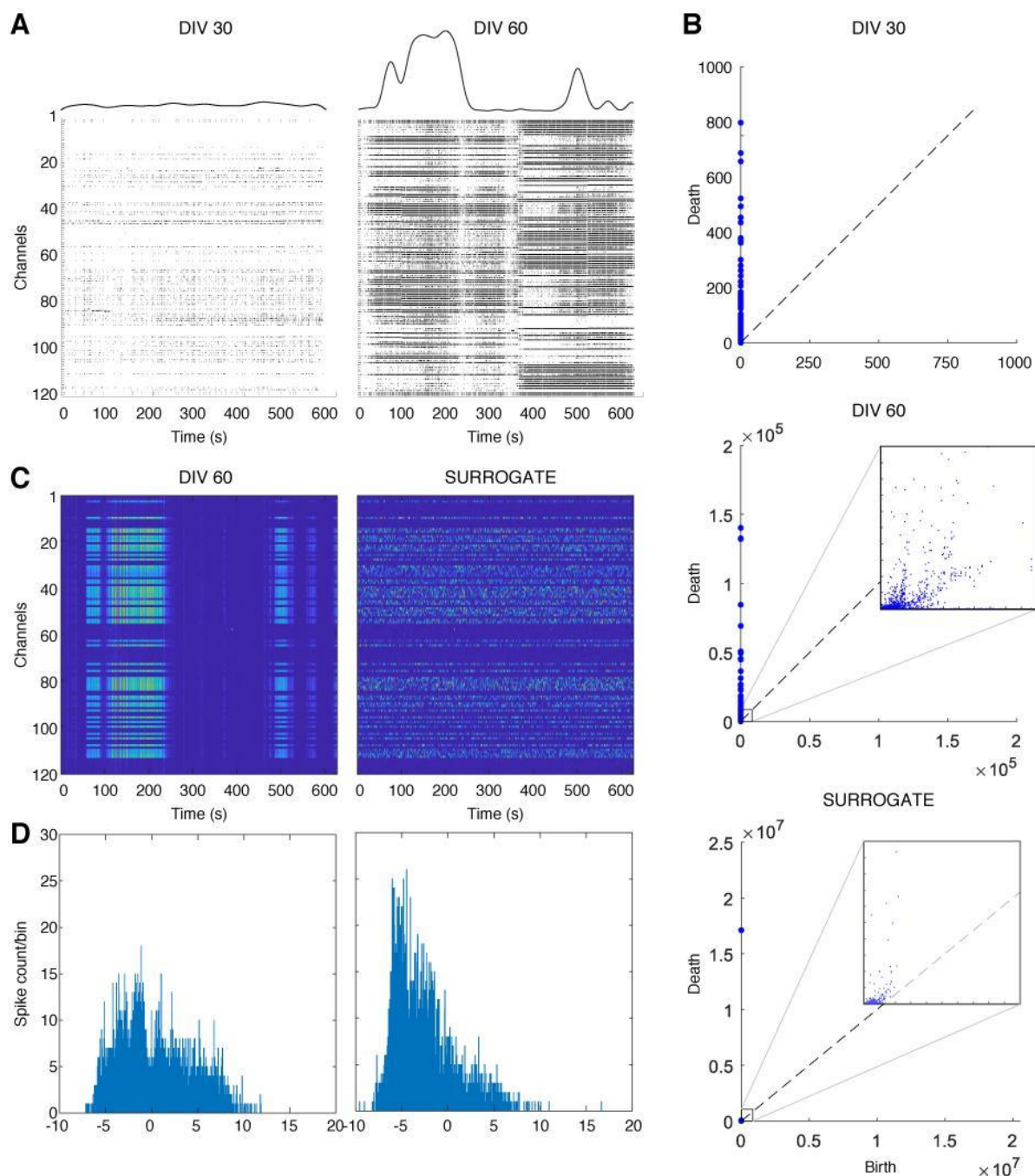
Title: Topological invariants in the activity of three-dimensional bioprinted neuronal constructs derived from human induced pluripotent stem cells

Authors: *C. S. SIMÕES¹, L. V. BIM¹, M. MARIANO DA SILVA², D. D. SILVA⁴, J. FABER³, M. A. PORCIONATTO¹;

¹Biochem., ²Biophysics, ³Neurol. and Neurosurg., Federal Univ. of São Paulo, São Paulo, Brazil;

⁴Mathematics, Federal Univ. of Sergipe, Aracaju, Brazil

Abstract: The mechanisms underlying circuit formation during neurodevelopment remain poorly understood, despite their crucial role in conditions such as autism spectrum disorder. In this exploratory study, we applied persistent homology—a topological data analysis technique—to investigate network connectivity during early stages of in vitro neuronal development, analyzing activity patterns in 3D bioprinted neuronal constructs derived from human induced pluripotent stem cells (hiPSCs). This approach enables the investigation of neurodevelopmental processes in a more physiologically relevant environment compared to traditional 2D cultures. Electrophysiological activity was recorded using a 120-channel microelectrode array (MEA2100, Multichannel Systems) for at least 5 minutes at both 30 and 60 days in vitro (DIV). Time series were band-pass filtered (100-3000 Hz), and spike peaks were detected. Multi-unit analysis revealed an overall increase in firing rate from DIV30 to DIV60 (figure 1A). To assess connectivity through persistent homology, spike count histograms (0.5 s bins) were smoothed using a Gaussian kernel and averaged across channels (fig. 1A top). A 3D phase space was reconstructed using vectors shifted by 0, 1, and 2 bins as the embedding matrix. Simplicial complexes were computed, and birth-death pairs of H0, H1, and H2 invariants were extracted. H2 invariants differed significantly between DIV30 and DIV60 (fig. 1B). To determine whether these differences were solely attributable to increased firing rates, DIV60 data were compared to a surrogate dataset (fig. 1C). Despite high variance, a Kolmogorov-Smirnov goodness-of-fit test on the birth-death distance distributions indicated significantly distinct patterns (fig. 1D, $=2.14 \times 10^{-140}$). These results suggest that connectivity emerges within developing neural tissue and contributes to the organization of increased and synchronous firing patterns, as captured by topological invariants of the recorded signal. New recordings from 90 and 120 DIV and from more batches of constructs will be acquired.



Disclosures: C.S. Simões: None. L.V. Bim: None. M. Mariano da Silva: None. D.D. Silva: None. J. Faber: None. M.A. Porcionatto: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.15/B50

Topic: B.07. Network Interactions

Support: Burroughs Welcome Fund 1015644
NIMH Grant R01MH123650
VA CESAMH Postdoctoral Fellowship

Title: Dynamic Oscillatory Motifs Link Local Field Potentials to Glutamatergic and GABAergic Activity in Rat Prelimbic Cortex

Authors: *J. MISHLER¹, M. SALIMI³, J. MISHRA⁴, D. RAMANATHAN^{5,2};

¹VA, San Diego, CA; ²VA, San Diego, CA; ³Univ. of California San Diego, San Diego, CA;

⁴Psychiatry, Univ. of California San Diego, La Jolla, CA; ⁵Psychiatry, UC San Diego, La Jolla, CA

Abstract: Understanding how population-level neural activity maps onto local field potentials (LFPs) remains a central challenge in systems neuroscience. To address this, we simultaneously recorded LFPs and cell-type-specific bulk calcium signals from glutamatergic (AAV5-CaMKII-GCaMP6f) and GABAergic (AAV9-CaMKII-GCaMP6f) neurons in the prelimbic cortex of rats using custom-fabricated optrodes. LFPs were bandpass filtered into narrow bands spanning delta to high gamma, then envelope-extracted and smoothed to match the temporal dynamics of the calcium signals. Across animals and sessions, we observed consistent cross-frequency correlations between filtered LFP amplitudes and calcium activity in both cell-types that evolved dynamically over time.

To quantify these correlational motifs, we applied a hierarchical clustering-based dimensionality reduction algorithm to the LFP-calcium correlations. The resulting low-dimensional motifs were present in each animal and exhibited structured transitions over time. Each motif reflected coordinated amplitude co-modulations across multiple frequency bands, rather than single bands alone. To assess behavioral relevance, we trained rats on a closed-loop fiber photometry brain-computer interface (BCI) task to volitionally downregulate glutamatergic or GABAergic calcium activity. With training, expression of one previously identified motif increased while another was suppressed. These findings demonstrate that LFP-calcium motifs are conserved, dynamic, and behaviorally modifiable, positioning them as potential mesoscopic markers of volitional circuit engagement.

Disclosures: J. Mishler: None. M. Salimi: None. J. Mishra: None. D. Ramanathan: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.16/B51

Topic: B.07. Network Interactions

Support: NIH Grant R01-GM056398
Department of Anesthesiology, University of Michigan Medical School

Title: Anesthetic State-dependent Dynamics of Traveling Waves in Rat Cerebral Cortex

Authors: *D. LI¹, A. G. HUDETZ²;

¹Univ. of Michigan, Ann Arbor, MI; ²Dept. of Anesthesiol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Introduction: Understanding how anesthesia alters cortical information flow is a promising approach to uncover the neural basis of consciousness. General anesthetics are thought to influence anteroposterior information flow as an indication of the state of consciousness. Electrocortical traveling waves may be a sensitive index of cortical information flow but their modulation by anesthesia remains underexplored. Temporal dynamics of cortical traveling waves may also be affected by spontaneous changes in neuronal activity that are common during general anesthesia. To examine how traveling waves are modulated across spontaneously changing cortical states, we recorded hemisphere-wide ECoG at varying depths of anesthesia and analyzed the dynamics of traveling waves as a function of cortical state and frequency band. **Methods:** ECoG was recorded from the right hemisphere with chronically implanted 32-ch flexible polymer electrode arrays (4×8 grid) at four inhaled concentrations (6%, 4%, 2%, 0%) of the volatile anesthetic desflurane for 1 h each. Cortical states were identified via principal component analysis of power spectrograms followed by density-based clustering. To account for spontaneous changes, cortical states were identified independently of the anesthetic concentration. Within each state, traveling wave candidates were identified as episodes of stable spatial phase gradient patterns in delta (0-4 Hz), theta (4-8 Hz), and gamma (25-55 Hz) bands, where temporal similarity exceeded that across more distant time points. Plane waves were classified as feedforward (posterior-to-anterior) or feedback (anterior-to-posterior) if the variance of their phase gradient direction fell below the 99th percentile of shuffled data. **Results:** Seven cortical states were identified. States S1-S5 broadly tracked anesthetic depth from 0% to 6%. S6 reflected electrocortical burst suppression. A paradoxical, activated state (S7) defined by its spectral similarity to the light anesthetic states emerged during deep anesthesia. S1 featured theta waves dominant in the feedback direction and gamma waves in the feedforward direction. Delta waves increased with anesthesia, while the occurrence of theta and gamma waves changed little. Notably, theta feedback dominance was suppressed in S4-S6 but reemerged in S7 while gamma feedforward dominance persisted in all states. **Conclusions:** Anesthesia alters cortical traveling waves in a frequency-specific manner. The loss of theta feedback dominance in deep anesthesia may reflect disrupted conscious processing. The implication of theta wave reemergence in the paradoxical state remains to be better understood.

Disclosures: D. Li: None. A.G. Hudetz: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.17/B52

Topic: B.07. Network Interactions

Support: CephRes-2021
HSA-Ceph 2019-1

Title: Characterize visual evoked potentials (VEPs) and resting state potentials (RSPs) of the optic lobe (OL) and supraoesophageal mass (SEM) non-invasively in lightly-sedated *Octopus vulgaris*

Authors: *M. DE LUCA^{1,2}, J. SCHMIDT³, C. CHIANDETTI⁴, G. FIORITO^{5,2}, G. PONTE^{5,2};
¹Stazione Zoologica Anton Dohrn - Napoli, Italy, Napoli, Italy; ²Assn. for Cephalopod Res. - CephRes ETS, Napoli, Italy; ³Univ. zu Koeln, Koeln, Germany; ⁴Univ. di Trieste, Trieste, Italy; ⁵Stazione Zoologica Anton Dohrn, Napoli, Italy

Abstract: Visual Evoked Potentials (VEPs) in vertebrates including humans has been widely used for elucidating mechanisms underlying visual information process of the brain and investigating neural correlates of high-level cognitive functions of animals. Non-invasive recording of VEPs from freely-moving or lightly-sedated animals has proven to be particularly valuable in revealing neural mechanisms of brain functions. Decades of researches have shown functional analogies between brain areas of cephalopod molluscs and vertebrates and demonstrated complex cognitive abilities in cephalopods comparable to those of vertebrates. To investigate the neural mechanisms in the octopus brain, we developed non-invasive electrophysiological method to record, for the first time, the VEPs and resting state potentials (RSPs) with 5 minute on and off diffused white light in lightly-sedated *Octopus vulgaris* (n=14; weight: 208-802 g) with Ag/AgCl subcutaneous electrodes (0.4 mm diameter) positioned at the top of the OLs and SEM. A blue LED, positioned in proximity (0.5 - 2 cm) of the eye, was used for delivering two patterns of light stimulations: a train of light pulses (0.1 s duration, 5 s inter-pulse interval) and a single pulse of 2 second duration. Reliable VEPs were recorded from both OL and SEM with both light stimulation patterns. Four distinctive types of VEP waveforms were found based on K-mean cluster analysis of the main peak amplitude and peak latency (OL: type 1 to 3 with similar peak amplitude but different latency, ~500, ~600, ~800ms, respectively. Type 4 with amplitude 50% lower than type 1-3 and broad latency ranging from 300 to 1000ms. SEM: type 1 to 3 with similar peak amplitude but different latency, ~50, ~175, ~200ms, respectively. Type 4 with amplitude 50% lower than type 1-3 and broad latency ranging from 250 to 270ms). Spectral analysis of the RSPs revealed an increase in power in all the classic frequency bands in human electroencephalography (EEG). Interestingly, in both light on and off conditions, the total power of the RSPs was mainly distributed across low frequency bands, i.e. Delta (0.5-4 Hz), Theta (4-8 Hz) and Alpha (8-12 Hz). Using a minimally invasive electrophysiological approach, the current study revealed first time that the VEPs and RSPs recorded in lightly-sedated octopus exhibited similar but distinctive properties comparing to those from mammals, indicating functional similarities and disparities of the central neural system of the octopus to the vertebrates. This approach therefore opened new doors for future investigation of the neural basis of the highly complex cognitive functions of the octopus brain.

Disclosures: M. De Luca: None. J. Schmidt: None. C. Chiandetti: None. G. Fiorito: None. G. Ponte: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.18/B53

Topic: B.07. Network Interactions

Support: Senior Fellowship from Department of Biotechnology(DBT)-Wellcome India Alliance (To Supratim Ray- Grant IA/S/18/2/504003)

Title: Differential burst dynamics of slow and fast gamma rhythms in macaque V1

Authors: *R. VIGNESH^{1,2}, S. RAY²;

¹Undergraduate Program, ²Ctr. for Neurosci., Indian Inst. of Sci., Bengaluru, India

Abstract: Gamma oscillations have been implicated in feature binding through synchronization, attention and other cognitive processes (Han et al., 2021; Gregoriou et al., 2009). They are known to be generated due to network interactions between excitatory and inhibitory populations of neurons. Recent studies have shown that large visual sinusoidal gratings elicit two distinct gamma rhythms, namely, slow (≈ 20 -35 Hz) and fast gamma (≈ 35 -65 Hz), in the primary visual cortex (V1) of non-human primates (Murty et al., 2018). Studies using optogenetics in mouse V1 have highlighted the specific roles of somatostatin (SOM) and parvalbumin-positive (PV+) inhibitory interneurons in generating slow and fast gamma, respectively (Veit et al., 2017). But how different interneuron classes influence network activity is not well understood. Furthermore, gamma rhythm has been observed to occur stochastically in the form of bursts in V1, rather than manifesting as sustained and continuous rhythmic activity (Chandran Ks et al., 2018). Analyzing the burst profiles of slow and fast gamma rhythms could provide valuable insights about the mechanisms by which they influence cortical activity. We therefore recorded local field potential (LFP) from V1 of two adult female bonnet monkeys performing a fixation task while viewing large gratings that induced both gamma rhythms. We then computed burst lengths of slow and fast gamma observed in the LFP recordings using the Matching Pursuit (MP) algorithm. We found that the slow gamma rhythm exhibited significantly longer burst lengths than fast gamma. The trend was conserved across different stimulus orientations. Even after performing power matching across electrodes, the difference was persistent, ruling out the possible bias due to power differences between the two rhythms. Slow gamma bursts also had longer latency compared to fast gamma. The results were consistent even when we used other methods based on the Wavelet transform, Orthogonal Matching Pursuit algorithm, and Hilbert transform to estimate burst lengths. These results are consistent with the hypothesis that slow-gamma is generated by the SOM network, where dendrite-specific inhibition (generating a slow-negative feedback) and slower kinetics of postsynaptic GABA_A receptors located on the dendrites of

pyramidal cells (Schulz et al., 2018) might be the plausible biophysical mechanisms behind increased latency and longer bouts of slow gamma. Longer burst durations could potentially aid slow gamma rhythm in serving as a global (long-range) modulatory signal. These burst signatures could also be used as putative biomarkers for diagnosing cognitive impairments.

Disclosures: R. Vignesh: None. S. Ray: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.19/B54

Topic: B.07. Network Interactions

Title: Interactions of single-neuron spiking with the spectrolaminar motif of LFP power via spike-field synchronization

Authors: *A. ABDALTAWAB^{1,2}, A. NILAJAGI¹, M. BABAEI³, Y. XIONG⁴, H. NEJAT⁴, A. BASTOS⁴, D. MENDOZA-HALLIDAY^{1,2};

¹Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; ²Neurosci., Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; ³Univ. of Tehran, Tehran, Iran, Islamic Republic of; ⁴Psychology and Vanderbilt Brain Inst., Vanderbilt Univ., Nashville, TN

Abstract: We recently reported the discovery of a robust motif of local field potential (LFP) power across cortical layers consisting of laminar gradients of gamma (>40 Hz) and delta/theta (1-8 Hz) LFP power peaking in superficial layers (2/3) and an opposite gradient of alpha/beta (10 Hz -30 Hz) power peaking in deep layers (5/6). This spectrolaminar motif is remarkably conserved across cortical areas, suggesting a ubiquitous cortical mechanism of columnar processing. Here we address two fundamental questions that emerge: first, is the spectrolaminar motif formed by multiple separate components of rhythmic activity? Second, what are the neuronal mechanisms that produce those rhythmic components? To address these questions, we first developed an LFP-level model based on the premise that the cortical LFP signals are the combination of an aperiodic 1/f background component and a finite number of separate periodic (rhythmic) components, each with a confined frequency range and laminar location. When supplied with three periodic components, the model reproduced the main features of the macaque spectrolaminar motif. We then applied our model to fit spectrolaminar power patterns from 100 laminar recordings from various macaque cortical areas from early visual (MT) to higher-level (LPFC) and varied the model's rhythmic components from one to eight. Goodness of fit (R^2 , RMSE) improved with additional components but saturated at and after three (mean $R^2 = 0.84 \pm 0.17$). K-means clustering of all fitted peak component frequencies consistently revealed three clusters centered within the delta/theta, alpha/beta, and gamma bands, indicating that a compact three-rhythm model captures 84% of spectral variance across cortical layers. To examine the neuronal mechanisms behind these rhythmic components, we used pairwise phase consistency to

quantify spike-field phase synchrony between single neuron spiking and these rhythmic components. Single neuron spiking synchronized with the gamma component only at channels around the neuron's vicinity. In contrast, laminar recordings showed one of three different profiles depending on where neurons' synchrony with the alpha/beta component peaked: (1) at the laminar location of the alpha/beta component's center regardless of the neuron's location, (2) in layers superficial to that center, and (3) around the neuron's vicinity. Together, these results suggest that the spectrolaminar motif reflects three rhythmic components in the cortex and suggest that the gamma component is produced by a more local neuronal circuit while the alpha/beta component is produced by anatomically broader and more complex neuronal interactions.

Disclosures: A. Abdaltawab: None. A. Nilajagi: None. M. Babaei: None. Y. Xiong: None. H. Nejat: None. A. Bastos: None. D. Mendoza-Halliday: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.20/B55

Topic: B.07. Network Interactions

Support: NIH RO1-MH125429
NIH R01NS119395

Title: Region-specific neural dynamics elicited by paired cortical optogenetic stimulation

Authors: *S. SHAN¹, G. SHVARTSMAN², A. YAZDAN-SHAHMORAD³;

¹Bioengineering, ²Neurosci., ³Bioengineering and Electrical Engin., Univ. of Washington, Seattle, WA

Abstract: Neuroplasticity is the brain's ability to adapt and reorganize in response to new stimuli. Since Donald Hebb's fundamental idea that 'neurons fire together wire together', numerous plasticity theories were proposed, including Kempter theory, which states that the expected synaptic weight change is proportional to the convolution of the pre-/post- spike train cross correlation with the plasticity rule learning kernel. Despite many proposed theories validated in the synaptic level, the influence of cortical structure on the plasticity rule remains unclear. The primary motor (M1) and somatosensory (S1) cortices exhibit distinct architecture and neuronal compositions. M1 contains predominantly large pyramidal neurons with long projections to subcortical targets, facilitating voluntary motor control. In contrast, S1 has well-defined columnar organization with a high density of spiny stellate cells and short-range connections, specialized for sensory processing and feedforward signaling. In this study, we investigated the plasticity response of M1 and S1 cortices respectively under the same stimulation protocol in two non-human primates. Through optogenetically targeting excitatory

neurons, we applied paired optical stimulation with varying time intervals between two randomly selected sites within each cortex for 10 minutes. We evaluate the network and local functional connectivity during spontaneous recording period before and after conditioning using a 96 channel ElectroCorticogram covering both M1 and S1. We observed different patterns for network synchronization and functional connectivity change after optical stimulation in M1 versus S1. Additionally, we observed that the functional connectivity change between stimulation sites was correlated to different plasticity learning kernel after applying Kempter's theory. Thus, this study shows the region-specific plasticity response, likely due to the distinct neuron composition and connectivity pattern in each cortex. This difference additionally indicates the need for developing a region-specific neuromodulation paradigm that accounts for the difference in circuitry to effectively induce a desired plasticity change.

Disclosures: S. Shan: None. G. Shvartsman: None. A. Yazdan-Shahmorad: None.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.21/B56

Topic: I.04. Executive Functions

Support: NIH Grant R01MH124387
NIH Grant R01MH122477

Title: Oscillatory coordination between posterior parietal cortex and caudate nucleus reveals cortico-striatal mechanisms of brain state regulation

Authors: *M. REAMES^{1,2,3,4}, G. ROSS^{1,2,3,4}, E. GHIM^{1,2,3,4}, G. SAHYOUN^{6,2,3,4}, S. RADTKE-SCHULLER^{1,2,4}, F. FROHLICH^{1,2,3,4,5};

²Psychiatry, ³Neurosci., ⁴Carolina Ctr. for Neurostimulation, ⁵Cell Biol. and Physiol., ¹Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; ⁶Univ. of North Carolina Chapel Hill Sch. of Med., Chapel Hill, NC

Abstract: Although traditionally associated with motor control, the dorsal striatum — a region of the basal ganglia composed of the putamen and caudate nucleus — has recently also been implicated in higher-level cognitive processes. The caudate nucleus (Cd) is of interest in the study of cognitive control given its anatomical projections to the fronto-parietal network (FPN), a circuit known to support cognitive control via rhythmic synchronization. However, the coordination of cortical-subcortical rhythmic activity remains poorly understood. This research sought to (1) identify how oscillatory activity in Cd contributes to sensory processing and changes across arousal level and (2) establish the presence of the rhythmic functional connectivity between Cd and the posterior parietal cortex (PPC) and its modulation by arousal indexed by pupil diameter. To address these questions, two head fixed female ferrets (*Mustela*

putorius furo) were presented with naturalistic videos while pupillometry (to index arousal), Cd and PPC electrophysiology recordings were collected. Ferrets were selected for this study due to neuroanatomical tracing evidence that the lateral caudate has convergent projections from the frontal and parietal nodes of the FPN, mirroring findings in non-human primates. Results showed distinct oscillations in the alpha and theta bands in Cd; where alpha power is modulated by arousal level, with lower arousal corresponding to higher alpha power. Measuring functional connectivity by phase locking value showed clear connectivity between Cd and PPC in both the alpha and theta bands. Like patterns previously observed in cortico-thalamic theta connectivity, alpha connectivity was most prominent at low arousal states while theta connectivity was dominant at high arousal states. Rhythmic optogenetic stimulation at the endogenous peak of alpha in PPC resulted in clear entrainment of PPC multi-unit activity and increased LFP power at stimulation frequency in both PPC and Cd. Optogenetic stimulation resulted in strengthening of connectivity between PPC and Cd at stimulation frequency. These results demonstrate state dependency of cortico-striatal connectivity for the first time and show that frequency-specific Cd connectivity can be enhanced with external stimulation. Our findings expand current understanding of Cd involvement in executive functions beyond motor control and suggest alpha as a general cortical-subcortical signature of top-down cortico-subcortical control, inhibition, and selective disengagement.

Disclosures: **M. Reames:** None. **G. Ross:** None. **E. Ghim:** None. **G. Sahyoun:** None. **S. Radtke-Schuller:** None. **F. Frohlich:** F. Consulting Fees (e.g., advisory boards); FF receives payments as a consultant from Electromedical Products International and Insel Spital, unrelated to the work presented here.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.22/B57

Topic: I.04. Executive Functions

Support: NIH Grant R01MH124387
NIH Grant R01MH122477
NIH Grant R34DA061924

Title: Hyperscanning the caudate nucleus in freely behaving ferrets to investigate its role in social behavior

Authors: ***G. SAHYOUN**^{1,2,3,4}, **G. ROSS**^{2,3,4}, **M. REAMES**^{2,3,4}, **E. GHIM**^{2,3,4}, **S. RADTKE-SCHULLER**^{2,3}, **J. REILING**⁷, **M. ZHANG**⁷, **F. FROHLICH**^{2,3,4,5,6};

¹Univ. of North Carolina Chapel Hill Sch. of Med., Chapel Hill, NC; ²Psychiatry, ³Carolina Ctr. for Neurostimulation, ⁴Neurosci. Ctr., ⁵Cell Biol. and Physiol., ⁶Neurol., Univ. of North Carolina

at Chapel Hill, Chapel Hill, NC; ⁷Computat. Mathematics, Sci. and Engin., Michigan State Univ., East Lansing, MI

Abstract: The basal ganglia are prominently associated with motor control; however recent evidence has proposed that a subregion, the caudate nucleus (Cd), may also have roles in “higher order” behaviors like cognition and social behavior. In primate studies, Cd neurons were more modulated by social reward than a liquid reward. In human fMRI studies, increased Cd activation was associated with positive vs negative social stimuli compared to negative. However, task-based examinations do not capture the complexity of true social behavior. Studies have begun to increasingly study the brain in complex, naturalistic settings using a technique called “hyperscanning”, where brain activity is simultaneously recorded in multiple individuals. These studies led to the discovery of interbrain synchronization in humans mediated by frontal theta oscillations (4-8Hz) and parietal alpha oscillations (8-12Hz) during various social behaviors. Traditional human electrophysiology methodologies used for hyperscanning (e.g. EEG) cannot effectively target subcortical regions like Cd. Thus, direct examination of Cd during complex naturalistic social behavior has not yet been done. Here, we introduce domestic ferrets (*Mustela putorius furo*) as a translationally relevant model for this line of inquiry. Ferrets exhibit strong social-cognitive skills and visuomotor communication. They have a neuroanatomically delineated Cd with overlapping terminal projections from both frontal and parietal cortices, mirroring the circuit organization of primates. They also exhibit human homologs of theta and alpha oscillations in the frontoparietal network during cognitive tasks. Our preliminary findings demonstrate that alpha oscillations in the posterior parietal cortex (PPC) mediate interbrain synchronization between two ferrets during bidirectional social interaction. Theta oscillations do so in unidirectional social interaction, identifying functional roles for both rhythms in social interaction. Given the converging terminal projections from both frontal and parietal cortices on Cd, we hypothesize that social interaction will differentially alter Cd-PPC connectivity in the theta/alpha frequency bands. In our ongoing work, electrophysiology from Cd and PPC is recorded simultaneously in pairs of ferrets during social interaction. With this, combined with behavior analysis coding epochs of socialization and inactivity, we will investigate Cd’s role in multiple aspects of social behavior, including interbrain synchronization. This work addresses a critical gap in research by investigating the role of cortico-striatal connectivity in naturalistic social behavior.

Disclosures: **G. Sahyoun:** None. **G. Ross:** None. **M. Reames:** None. **E. Ghim:** None. **S. Radtke-Schuller:** None. **J. Reiling:** None. **M. Zhang:** None. **F. Frohlich:** A. Employment/Salary (full or part-time): Electromedical Products International, Insel Spital.

Poster

PSTR007: Oscillatory, Aperiodic, and Waveform Analyses of Electrophysiological Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR007.23/B58

Topic: I.04. Executive Functions

Support: R01MH124387
R01MH122477

Title: Increased sustained attention and neuronal entrainment by rhythmic optogenetic stimulation of the dorsal fronto-parietal network

Authors: *G. ROSS¹, W. A. HUANG², M. ZHANG⁴, S. RADTKE-SCHULLER³, J. B. HOPFINGER⁵, F. FROHLICH⁶;

¹Univ. of North Carolina Chapel Hill, Chapel Hill, NC; ²Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; ³Dept. of Psychiatry, Univ. of North Carolina At Chapel Hill, Diessen am Ammersee, Germany; ⁴Computat. Mathematics, Sci. and Engin., Michigan State Univ., East Lansing, MI; ⁵Dept. of Psychology, Univ. of North Carolina, Chapel Hill, NC; ⁶Psychiatry, Univ. of North Carolina, Chapel Hill, NC

Abstract: Introduction: Synchronization of the dorsal frontoparietal network (dFPN) is orchestrated by theta oscillations during sustained attention. Reduced theta connectivity within the dFPN correlates with attentional fluctuations during a preclinical sustained attention task under high cognitive demand. However, causal perturbation of dFPN theta oscillations during sustained attention is required to establish a causal relationship. Methods: To test whether dFPN theta connectivity causally supports sustained attention, we applied rhythmic optogenetic stimulation to the frontal node of the ferret dFPN during the 5-Choice Serial Reaction Time Task (5-CSRTT). Sustained attention is engaged during the delay period of the 5-CSRTT, which was lengthened to increase cognitive demand. Optogenetic stimulation was applied at endogenous theta (5 Hz), high-theta (11 Hz) or not at all (sham) during the short- or long-delay (more cognitively demanding) 5-CSRTT condition. Single unit activity and local field potentials were recorded from the premotor cortex (PMC) and posterior parietal cortex (PPC), comprising the ferret dFPN, during the 5-CSRTT. Results: Extending the 5-CSRTT delay period significantly lowered task accuracy ($b = -16.6$, $df(52.9) = -5.6$, $p < 0.001$), reduced PMC theta oscillations and led to a desynchronization of dFPN theta connectivity. Optogenetic stimulation drove PMC single-unit activity and increased local field potential power at stimulation frequencies. Contrary to initial predictions, high-theta stimulation enhanced dFPN connectivity more than theta-stimulation, in both short- and long-delay conditions (short: $b = -0.15$, $df(49.9) = -5.2$, $p < 0.001$, long: $b = -0.11$, $df(28.0) = -3.3$, $p = 0.003$). High-theta stimulation increased accuracy ($b = 4.8$, $df(78.9) = 2.4$, $p = 0.02$) and lowered reaction time ($b = -0.09$, $df(80.9) = -2.2$, $p = 0.03$) in the short-delay condition, but had no behavioral effect in the long-delay condition. Theta-stimulation had no significant effect on behavior. Attentional fluctuations were assessed by quantifying variation in reaction time within session and found to be unaffected by high-theta stimulation in the short-delay condition ($b = 0.03$, $df(78.3) = 0.98$, $p = 0.33$). This suggests dFPN high-theta connectivity plays a distinct causal role from the previously established functional role of dFPN theta connectivity in the 5-CSRTT. Conclusion: Results demonstrate frequency- and state-dependent effects of optogenetic stimulation in entraining network activity and affecting behavior. These results emphasize that stimulation interventions must consider both oscillatory and cognitive states to be most effective.

Disclosures: G. Ross: None. W.A. Huang: None. M. Zhang: None. S. Radtke-Schuller: None. J.B. Hopfinger: None. F. Frohlich: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.01/B59

Topic: B.08. Epilepsy

Support: NIH NINDS RO1 NS119977
March of Dimes
Linse/Heckert Family

Title: A novel mouse model of SCN3A-related neurodevelopmental disorder

Authors: *M. SHERER^{1,2}, E. M. GOLDBERG^{5,6,3,4},
¹Neurosci., Univ. of Pennsylvania, Philadelphia, PA; ²Neurosci. Grad. Group, ³Neurol.,
⁴Neurosci., Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA; ⁵Neurol., ⁶The
Epilepsy Neurogenetics Initiative, The Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: *SCN3A*-related neurodevelopmental disorder (*SCN3A*-NDD) is caused by heterozygous pathogenic variants in the gene *SCN3A* encoding the voltage gated sodium (Na⁺) channel subunit Nav1.3, which is highly expressed in the embryonic nervous system. *SCN3A*-NDD is associated with three core clinical features including: early onset treatment-resistant epilepsy, developmental delay/intellectual disability (DD/ID), and ~50% of patients present with malformation of cortical (MCD). Prior characterization in heterologous systems revealed that pathogenic Nav1.3 variants broadly exert gain of function effects marked by an increase in slow inactivating/persistent Na⁺ current (I_{NaP}), a left shift in the voltage dependence of activation, and/or prolongation of the time constant of fast inactivation. However, the functional role of Nav1.3 has been largely understudied and given the recent identification of *SCN3A*-NDD, disease mechanisms remain unclear and there currently exists no treatment or cure. To address this, we developed a novel preclinical mouse model. The Cre-dependent *Scn3a*-Flox(V1721A)/+ knock-in mouse line conditionally expresses an *Scn3a*-p.V1721A allele homologous to the recurrent pathogenic *de novo* human variant *SCN3A* c.5306T>C (p.Val1769Ala) associated with epileptic encephalopathy and severe/profound DD/ID but without MCD. We cross a dam homozygous for *Scn3a*-Flox(V1721A) to a heterozygous Snap25-Cre male resulting in *Scn3a*-p.V1721A/+ (“A/+”) mice and WT (+/+) littermate controls. Aligned with clinical observations, A/+ mice exhibit delayed growth, spontaneous seizures confirmed via electroencephalogram (EEG) monitoring, and premature mortality. We then employed whole-cell current clamp recordings in acute brain slices (P4-6, P8-10, P18-21) to establish the effects of variation in *Scn3a* on the intrinsic properties and firing patterns of cortical and hippocampal pyramidal neurons across development. We found A/+ neocortical pyramidal cells exhibit initial elevated firing frequency with low current injection followed by rapid entry into depolarization block with instances of plateau-like potentials. Compared to WT, A/+ CA1 pyramidal neurons exhibit a more depolarized resting membrane potential, show spontaneous firing patterns, and discharge prolonged action potentials. Our findings provide insight into the effect of epilepsy-associated variants in *Scn3a* on cellular physiology. Further investigation using our mouse model will enhance knowledge of the functional role of Nav1.3 in the regulation of neuronal excitability,

brain development, and disease, and advance effective therapeutic interventions for *SCN3A*-NDD.

Disclosures: M. Sherer: None. E.M. Goldberg: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.02/B60

Topic: B.08. Epilepsy

Support: SNSF Grant P2LAP3_199556
 NINDS Grant NS34774

Title: Beyond seizure control: identifying deficits in cognitive networks in absence seizure.

Authors: *G. VANTOMME, G. DEVIENNE, J. HULL, J. R. HUGUENARD;
Stanford Univ., Palo Alto, CA

Abstract: Typical absence seizures are characterized by sudden, frequent episodes of unconsciousness that persist for a few seconds, and predominantly affect children. These seizures typically stop naturally by adolescence, and two-thirds of affected children benefit from drug treatments that help control these seizures. Notwithstanding the success of such treatments, patients often experience persistent deficits in attention, memory, and general cognitive functions that are resistant to drugs. Our research sought to determine whether circuits essential for cognition show deficits in a model of absence seizures. Through this investigation, we aim to uncover how network connectivity evolves and identify potential new targets to alleviate associated comorbidities. Our approach uses a combination of optogenetic stimulation with electrophysiological recordings at single cell and network levels in vitro, and silicon multi-electrode array recordings in vivo, in a *Scn8a* hemi-deletion mouse model. We discovered deficiencies in thalamic Reunions inputs to Layer 5 pyramidal cells in the medial prefrontal cortex, a region implicated in higher cognitive functions. These deficiencies were highlighted by changes in depolarization dynamics, synaptic integration, and balance between excitation and inhibition. Intriguingly, seizure generation did not occur upon optogenetic stimulation of the Reunions, which contrasts with clear seizure initiation when somatosensory thalamus was stimulated, supporting the idea that this circuit, important for cognition, is not part of the seizure generation network, per se. In summary, we identified changes in functional connectivity from the Reunions to the medial prefrontal cortex circuit within an absence seizure mouse model. Despite these deficits, the circuit does not directly contribute to seizure generation, but is likely to contribute to cognitive deficits reported in patients afflicted with absence seizures.

Disclosures: G. Vantomme: None. G. Devienne: None. J. Hull: None. J.R. Huguenard: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.03/C1

Topic: B.08. Epilepsy

Support: NIH Grant R01NS120973

Title: Wnk-spak/osr1 signaling pathway modulates neuronal chloride homeostasis, gaba signaling, and ictogenesis

Authors: *V. I. DZHALA¹, A. CARROLL¹, K. J. STALEY²;

¹Massachusetts Gen. Hosp., Charlestown, MA; ²Massachusetts Gen. Hosp., Boston, MA

Abstract: Chloride-permeable GABAergic signaling is the primary inhibitory synaptic system in the brain, and its failure leads to multiple neurological diseases, including recurrent seizure activity. Brain injury and seizures induce large transmembrane chloride influxes that elevate neuronal chloride concentration ($[Cl^-]_i$). The increased $[Cl^-]_i$ changes the driving force for transmembrane Cl^- currents, leading to depolarizing GABA responses that foster seizures and anticonvulsant resistance via failure of GABAergic inhibition. Under these conditions, inhibition of the Cl^- -accumulating $Na^+-K^+-2Cl^-$ co-transporter (NKCC1) and/or activation of the Cl^- -extruding K^+-Cl^- co-transporter (KCC2) should improve neuronal chloride homeostasis, GABAergic inhibition, and control of electrographic seizures. NKCC1 and KCC2 are stimulated and inhibited, respectively, by direct phosphorylation mediated by the Cl^- -sensitive WNK-SPAK/OSR1 kinase complex. We determined the net effects of WNK-SPAK/OSR1 catalytic activity inhibitors WNK463 and STOCK1S-50699 that reciprocally inhibit NKCC1 and activate KCC2 activity on $[Cl^-]_i$ elevation and extrusion rates during spontaneous ictal-like discharges (ILDs), and the correlation between ionic and electrographic effects in an *in vitro* model of post-traumatic epileptogenesis. We found that: (i) WNK463 progressively reduced elevated $[Cl^-]_i$ in injured neurons, reduced Cl^- rise time and enhanced Cl^- extrusion rates during ILDs; (ii) WNK463 abolished recurrent ILDs; (iii) WNK463 had no effects in the presence of GABA_A-receptor antagonist or CCCs inhibitors; (iv) STOCK1S-50699 reduced baseline $[Cl^-]_i$ and ILD frequency but exhibited acute neurotoxicity. Our findings demonstrate that mutual NKCC1 inhibition and KCC2 activation via the regulatory WNK-SPAK/OSR1 pathway exerts powerful anti-ictal effects by facilitating $[Cl^-]_i$ extrusion and provide a coherent understanding of the role of WNK-SPAK/OSR1 kinase and cation-chloride co-transport activity in neuronal chloride homeostasis, GABA signaling and ictogenesis.

Disclosures: V.I. Dzhala: None. A. Carroll: None. K.J. Staley: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.04/C2

Topic: B.08. Epilepsy

Title: Genetic causes of epilepsy and therapeutic targets for CDKL5 Deficiency Disorder:
Exploring CDKL5-mediated phosphorylation in synaptic formation, function, and plasticity

Authors: S. HORTON, S. K. ULTANIR;
The Francis Crick Inst., London, United Kingdom

Abstract: The brain consists of billions of neurons that communicate via trillions of specialized synaptic connections. Synapse formation occurs in a highly regulated spatiotemporal manner, yet synapses remain plastic, adapting over time to support key cognitive functions such as memory and learning. Disruptions in synapse formation and plasticity are increasingly implicated in neurodevelopmental and neurological disorders including autism spectrum disorder (ASD), schizophrenia, and epilepsy. One such disorder, CDKL5-deficiency disorder (CDD), is a leading genetic cause of early-onset epilepsy, with a prevalence of approximately 1 in 40,000-60,000 live births. Although synaptic dysfunction is a hallmark of CDD, the mechanisms by which CDKL5 mutations lead to synaptic abnormalities remain unclear. Most pathogenic mutations affect the kinase domain of CDKL5, implicating impaired phosphorylation of downstream targets in CDD pathology. Our lab has recently identified novel substrates of CDKL5, several of which are synaptic proteins previously linked to epilepsy and other neurodevelopmental disorders. One particularly interesting substrate is Syngap1, an abundant postsynaptic density protein and a key regulator of synaptic plasticity. Given that SYNGAP1 mutations cause epilepsy and intellectual disability, we hypothesize that CDKL5-mediated phosphorylation of Syngap1, and potentially other synaptic substrates, is critical for neurotypical synaptic development and function. Using a multidisciplinary approach including immunocytochemistry, chemical long-term potentiation (cLTP), live neuronal imaging, and super resolution microscopy we are investigating how CDKL5 regulates synaptic formation and plasticity via the phosphorylation of key synaptic proteins, in order to elucidate its role in CDD pathology. We anticipate that this research may offer insights into novel therapeutic targets for CDD and related disorders.

Disclosures: S. Horton: None. S.K. Ultanir: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.05/C3

Topic: B.08. Epilepsy

Support: K08 NS121599-01
R35 NS116852-05

Title: Real-time imaging of neuronal mitochondrial calcium buffering with cellular resolution during hippocampal seizures

Authors: *S. GRANAK¹, L. A. LAU², V. I. DZHALA³, K. P. LILLIS⁶, B. J. BACSKAI⁷, M. SANCHEZ-MICO⁸, K. J. STALEY⁴, M. McNALLY⁵;

¹Massachusetts Gen. Hosp., Boston, MA; ²Neurol. Res., Massachusetts Gen. Hosp., Melrose, MA; ³Dept. of Neurol., Massachusetts Gen. Hosp., Charlestown, MA; ⁴Neurol., Massachusetts Gen. Hosp., Boston, MA; ⁵Massachusetts Gen. Hosp., Charlestown, MA; ⁶Neurol., Harvard Med. School, MGH, Charlestown, MA; ⁷Dept Neurol., Mass Gen. Hosp., Charlestown, MA; ⁸Dept. of Neurol., Massachusetts Gen. Hosp. (MGH) / Harvard Med. Sch. (HMS), Charlestown, MA

Abstract: Mitochondria play an important neuroprotective role buffering large increases in cytoplasmic calcium (Ca) during seizures, where mitochondrial Ca dysregulation contributes to synaptic hyperactivity and excitotoxicity. However, tools to measure mitochondrial Ca handling in living tissue with cellular resolution have been limited. Here, for the first time, we employ novel two-photon (2P) imaging techniques to measure both neuronal cytoplasmic and mitochondrial Ca buffering during hippocampal seizures in vitro. Organotypic hippocampal slice cultures were prepared from P6-8 C57BL/6J mouse pups of both sexes and transduced with AAV2/9.Syn.NES-jRGECO1a and AAV2/8.hSyn.2mtYC3.6 permitting neuronal co-expression of a red cytoplasmic Ca indicator (jRGECO) and a mitochondrial-matrix-targeted ratiometric Ca sensitive fluorophore (Yellow Cameleon 3.6). Neuronal co-expression was confirmed with immunohistochemistry. Slices develop spontaneous, recurrent seizures within 1 week. Longitudinal 2P imaging of seizing CA1 pyramidal neurons was performed from DIV8 to DIV17 to assess dynamic Ca changes concurrently in neuronal cytosolic and mitochondrial compartments (λ_{ex} 915nm, 1.27 Hz). All image analyses were carried out using ImageJ, and data analyses were performed using MATLAB, Origin, and Prism. Neuronal ictal cytoplasmic Ca load increases with longer seizure duration (n = 7 slices, 46 neurons, 24 seizures; linear regression, $R^2=0.41$, $p<0.00$). At DIV8, there is a trend where ictal mitochondrial Ca buffering increases with longer seizure duration (n=3 slices, 20 neurons, 8 seizures; linear regression, $R^2=0.38$, $p=0.1$). However, at DIV11-13, longer seizures are observed and this relationship is reversed with less ictal mitochondrial Ca buffering during longer seizures (n=2 slices, 15 neurons, 7 seizures; linear regression, $R^2=0.58$, $p=0.04$). For the first time, we were able to concurrently image mitochondrial and cytoplasmic Ca dynamics during seizures in individual neurons. We found that neuronal somatic mitochondrial Ca buffering of cytoplasmic Ca during seizures varies over time. This may represent normal developmental maturation of mitochondrial Ca handling or emerging mitochondrial dysfunction due to increasing seizure burden or slice age. Whether these changes are adaptive/neuroprotective versus pathological and contributing to seizure-related excitotoxicity remain to be discovered. With these newly developed tools, we can now test these hypotheses with the necessary temporal and spatial resolution permitting new insights into the role of mitochondrial Ca handling during seizures.

Disclosures: S. Granak: None. L.A. Lau: None. V.I. Dzhalal: None. K.P. Lillis: None. B.J. Bacskai: None. M. Sanchez-Mico: None. K.J. Staley: None. M. McNally: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.07/C4

Topic: B.08. Epilepsy

Support: Medical Research Council, UK

Title: L-aspartate signalling in the brain and mechanisms of seizure generation.

Authors: *A. KIBE¹, N. E. DALE⁴, J. SZETO², M. J. WALL³;

¹Sch. of Life Sci., ³Life Sci., ²Univ. of Warwick, Coventry, United Kingdom; ⁴Univ. Warwick, Coventry, United Kingdom

Abstract: The enzyme asparagine synthetase (ASNS), which converts L-Aspartate (L-Asp) to L-Asparagine (L-Asn) is responsible for *de novo* synthesis of L-Asn in the brain. Mutations in ASNS cause microcephaly and intractable epileptic-like seizures. As L-Asp is the main substrate for ASNS, reductions of ASNS activity increases levels of intracellular L-Asp that could be released into the extracellular space. We hypothesized that accumulation of L-Asp may trigger seizure like activity through its known agonist action on NMDA receptors. We found that ASNS is strongly expressed in the cell bodies and terminals of hippocampal GABAergic interneurons as it colocalizes with both glutamate decarboxylase (GAD) and vesicular glutamate transporter 3 (VGLUT3), which is expressed only in the expressing cholecystokinin positive (CCK+) subset of GABAergic interneurons. The intensity of ASNS staining was higher in the hippocampal CA3 region compared to CA1 region. By recording field excitatory post-synaptic potential (fEPSPs) in area CA1 evoked by stimulation of the Schaffer Collaterals in mouse hippocampal slices, we found that inhibition of ASNS by L-albizzine (L-Alb) depressed synaptic transmission (n=12) and also triggered spontaneous seizure-like activity (10/14 slices). The effects of L-Alb on synaptic transmission inhibition could be blocked by 2-Amino-5-phosphonopentanoic acid (D-AP5), an NMDA receptor antagonist (n=6, $p < 0.0001$, Mann-Whitney U test). The effect of L-Alb on inducing seizure-like activity was also prevented by D-AP5 (n=10, Chi-squared test; $p = 0.0005$, $X^2 = 12.24$, degrees of freedom = 1). The synaptic transmission depression effect of L-Alb was inhibited in the presence of lanthanum chloride (LaCl₃), a hemichannel blocker (n=8, $p < 0.0001$, Mann-Whitney U test) suggesting channel-mediated release of L-Asp. We directly tested whether inhibition of ASNS causes the release of extracellular L-Asp in hippocampal slices, by using an electrochemical L-Asp biosensor. L-Alb reversibly increased the concentration of extracellular L-Asp (5/10 slices), particularly in area CA3. We found that theta burst stimulation of the Schaffer Collaterals can trigger activity-dependent release of L-Asp which was significantly higher in the CA3 region (Wilcoxon test, $p = 0.002$, n=11). Our findings suggest that the intracellular enzyme ASNS is a key determinant of extracellular L-Asp concentration particularly in area CA3. This contributes to understanding new potential mechanisms of epilepsy and suggests that countering excessive release of L-Asp may be a new therapeutic approach to control seizures in people in whom current medications are ineffective.

Disclosures: A. Kibe: None. N.E. Dale: None. J. Szeto: None. M.J. Wall: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.08/C5

Topic: B.08. Epilepsy

Title: Developing a functional in vitro assay of neuronal hyperexcitability for anti-epileptic drug discovery.

Authors: *S. GRIGORYEV, M. HE, D. LIU, C. PETROSKI, R. E. PETROSKI;
Neuroservices-alliance, San Diego, CA

Abstract: Neuronal hyperexcitability is a hallmark of epilepsy and some neurodevelopmental disorders. This phenomenon arises from an imbalance between excitatory and inhibitory signaling in neural networks. Currently, therapeutic interventions, include antiepileptic drugs and neuromodulation approaches to restore excitatory-inhibitory balance. Understanding the mechanisms of E-I balance and the dysregulation in pathological states is critical for developing new therapies. Primary cultures comprised of glutamatergic and GABAergic neurons form functional excitatory and inhibitory connections. Electrophysiology assays and can be used to interrogate E-I balance in these cultures. Neuronal hyperexcitability *in vitro* can be provoked using experimental methods used to study epilepsy/seizure *in vivo* such as GABA_A antagonists and kainic acid. Additional stimuli include KCl depolarization and the potassium channel blocker 4-aminopyridine. We will compare and contrast the network responses to these proconvulsant stimuli as well as the effects of known antiepileptic drugs in an effort to validate the *in vitro* model for assessing the efficacy of new therapeutic approaches for treating epilepsy and neurodevelopmental disorders.

Disclosures: S. Grigoryev: None. M. He: None. D. Liu: None. C. Petroski: None. R.E. Petroski: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.09/C6

Topic: B.08. Epilepsy

Support: DoD PR221869

Title: Effects of dual orexin antagonist sleep-aid treatment on posttraumatic seizures and GABAergic inhibition

Authors: Y.-Z. PAN¹, A. L. GOFORTH¹, S. M. OSTING¹, R. K. MAGANTI¹, *M. V. JONES²;

¹Neurol., ²Neurosci., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Traumatic brain injury (TBI) affects ~5.3 million Americans, with consequences including sleep disturbances, posttraumatic epilepsy (PTE), mood disorders (PTSD) and cognitive problems. There is a bidirectional relationship between sleep disorders and epilepsy as well as mood disorders. They can exacerbate each other, possibly causing disease progression. We previously showed that treatment with a dual orexin antagonist (DORA) can suppress posttraumatic seizures, enhance sleep homeostatic drive and GABAergic inhibition. Here, we assess more comprehensively the effects of DORA treatment on PTE and on GABAergic tonic and phasic inhibition in dentate gyrus granule cells. CD-1 mice (male and female, ~3 months old) underwent a craniotomy with delivery of a TBI (controlled cortical impact, CCI) or a craniotomy alone as sham injury. Animals also underwent EEG/EMG electrode implantation allowing continuous recordings for 6 weeks to record seizures and sleep, while being treated daily at 8 am via oral gavage with an FDA-approved DORA (Lemborexant, Eisai Inc) at 100mg/kg (or vehicle). Daily treatment continued while behavioral testing was performed in weeks 7 and 8 and slice patch clamp electrophysiology was performed in dentate granule cells in week 9 using standard ACSF and a KCl-based intracellular solution. Seizures were manually scored whereas interictal spikes were analyzed with an automated algorithm. 30% of animals receiving TBI developed spontaneous seizures across 6 weeks of recording. 5% of sham controls also developed spontaneous seizures. TBI mice treated with Lemborexant had seizures in week 1 only whereas vehicle-treated TBI had seizures throughout other weeks. 7/11 (63%) vehicle-treated mice had seizures whereas only 2/10 (20%) Lemborexant-treated mice had seizures. However, in mice with seizures, there were no differences in seizure frequency. The vehicle-treated group had more frequent interictal spikes than the Lemborexant group. GABAergic tonic currents were measured in voltage clamp by perfusion of 100 μ M bicuculline in the presence of 5 μ M GABA. There were no significant differences in tonic currents between sham vehicle (7 cells from 3 mice), sham Lemborexant (9 cells from 3 mice), TBI vehicle (15 cells from 4 mice) or TBI Lemborexant groups (9 cells from 3 mice). Analysis of mIPSCs is in progress. Our data thus far show that DORA treatment can suppress posttraumatic seizures and interictal spiking after TBI without altering GABAergic tonic inhibition in granule cells.

Disclosures: Y. Pan: None. A.L. Goforth: None. S.M. Osting: None. R.K. Maganti: None. M.V. Jones: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.10/C7

Topic: B.08. Epilepsy

Support: NIH NINDS 1R01NS136434
NIH NINDS 1R01NS137603

Title: Hypoosmolar Conditions Produce a Unique Pattern of Hyperexcitability in Adult CA1 Hippocampal Neurons

Authors: *A. BILAS¹, R. RIVAS¹, W. DEWING¹, D. K. BINDER², T. A. FIACCO³;
¹Univ. of California Riverside, Riverside, CA; ²Univ. of California Riverside Div. of Biomed. Sci., Riverside, CA; ³Cell Biol. & Neurosci., UC Riverside, Riverside, CA

Abstract: Rapid onset cellular edema in the brain leads to a reduction of the brain's extracellular space (ECS) and increases neuronal excitability. Rapid cell swelling and ECS constriction is a critical factor underlying hyperexcitable conditions including epilepsy. Using whole-cell patch clamp electrophysiology, we recorded electrical currents in CA1 pyramidal neurons in live hippocampal slices from mice. In adult mice (P56-84), but not in juveniles (P15-P21), there emerges a pattern of activity with some similarity to the ictiform activity commonly observed in epilepsy, even in the presence of tetrodotoxin to prevent neuronal firing. The ictiform bursts are observable in 30% - 40% hypoosmolar artificial cerebrospinal fluid (ACSF), but not in 17% hypoosmolar ACSF. The epileptiform bursting patterns are absent in juvenile mice, even in the presence of 40% hypoosmolar ACSF. Additionally, this activity does not appear to be appreciably impacted by the neuronal volume regulated anion channel (VRAC). VRAC is an outwardly-rectifying anion channel which primarily allows for the movement of chloride out of cells, creating an osmotic gradient that leads to a reduction in cellular volume. Using a *NEX1*-Cre promoter, we have selectively ablated the *SWELL1* gene which encodes for the essential LRRC8A subunit of VRAC, in cortical neurons. Despite the potential dysregulation of neuronal volume, these cells do not display a substantial increase in ictiform-like activity when compared to control animals. Conversely, our data suggests that targeted knockout of neuronal VRAC reduces the frequency of synaptic events, with small events (mEPSCs) being the most substantially diminished. We are performing additional experiments across a host of conditions to determine if activity of neuronal VRAC is context dependent. Overall, our results present an interesting avenue for further investigation into the impacts of both age and degree of swelling on neuronal hyperexcitability, as well as the role of neuronal VRAC in epileptiform conditions.

Disclosures: A. Bilas: None. R. Rivas: None. W. Dewing: None. D.K. Binder: None. T.A. Fiacco: None.

Poster

PSTR008: Epilepsy: Molecular and Synaptic Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR008.11/C8

Topic: B.08. Epilepsy

Support: NIH NINDS R01NS133169
Dravet Syndrome Foundation

Title: Chronic Restraint Stress alters BNST Synaptic Neurotransmission in a Dravet Syndrome Mouse Model

Authors: *E. HONG¹, G. BARROCAS¹, E. XU¹, W. P. NOBIS²;
¹Vanderbilt Univ. Med. Ctr., nashville, TN; ²NEUROLOGY, Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Stress is a well-recognized seizure precipitant in individuals with epilepsy. Individuals with Dravet Syndrome (DS) exhibit a high prevalence of neuropsychiatric comorbidities and respond differently to stress compared to other childhood epilepsies. Our previous work in *Scn1a*^{+/-} (DS) mice showed an altered baseline synaptic transmission in the bed nucleus of the stria terminalis (BNST) neurons. The BNST is a critical region for processing stress signals and modulating the hypothalamic-pituitary-adrenal axis, which regulates corticosterone (CORT) levels in rodents. To investigate how stress impacts DS mice, we determined how chronic restraint stress (CRS) alters body weight, serum CORT levels, and synaptic transmission in the BNST of DS mice compared to wild-type (WT) littermates. We hypothesize that prolonged CORT exposure will exacerbate the existing circuit dysregulation in DS mice, leading to maladaptive physiological and synaptic adaptations. Male and female *Scn1a*^{+/-} (DS; n=19) and WT (n=13) littermates (P18-P26) were assigned to either no handling (control) or 2 hours/day restraint for 8 days. Body weight was recorded daily, and CORT levels were measured on day 1 and day 8. On day 9, coronal slices containing the anterior BNST were prepared for whole-cell voltage clamp recordings. We recorded sEPSCs at -65 mV and sIPSCs at +10 mV. Under control conditions, DS mice weighed less than WT mice (genotype effect: $F(1,7)=11.0, p=0.01$). CRS reduced weight in WT mice (treatment effect: $F(1,16)=6.46, p=0.02$), but not in DS mice. Both stressed WT and DS mice had elevated CORT levels (treatment effect: $F(2,37)=12.3, p<0.0001$). Voltage clamp recordings revealed a genotype $\times$ treatment interaction on sEPSC amplitude ($F(1,57)=9.7, p<0.01$), and post hoc analysis showed that stressed DS mice had larger sEPSC amplitudes than DS controls ($p=0.01$) and stressed WT mice ($p<0.01$). sEPSC frequency also showed a genotype $\times$ treatment interaction ($F(1,51)=6.15, p=0.02$), with stressed WT mice having fewer events ($p<0.05$). sIPSC amplitudes remained unchanged, but sIPSC frequency showed a genotype $\times$ treatment interaction ($F(1,54)=5.75, p=0.02$), with stressed WT mice having more events than WT controls. These findings suggest that CRS elicits a distinct physiological and synaptic response in DS mice, potentially due to impaired parvalbumin interneuron function in forebrain circuits that project to the BNST. Stressed DS mice showed increased excitatory synaptic drive, whereas stressed WT mice had increased inhibitory synaptic drive that was not present in stressed DS mice. Overall, this could suggest neurocircuit changes that differentiate how DS mice respond to stress.

Disclosures: E. hong: None. G. Barrocas: None. E. Xu: None. W.P. Nobis: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.01/C9

Topic: B.09. Glial Mechanisms

Support: NIH P01AG078116-01

Title: Modulation of GLT-1 expression in astrocytes: consequences for neurovascular coupling, calcium network dynamics, and the blood-brain barrier

Authors: *B. E. WEISS¹, J. GOLLIHUE², E. B. RUCKER, III³, C. B. ROGERS¹, J. C. GANT¹, S. D. KRANER⁴, C. M. NORRIS¹;

¹Sanders-Brown Ctr. on Aging, ²Sanders Brown Ctr. on Aging, ³Dept. of Pharmacol. and Nutritional Sci., ⁴Univ. of Kentucky, Lexington, KY

Abstract: Background: Astrocytes protect neuronal circuits by clearing synaptic glutamate via GLT-1 (EEAT2), maintaining metabolic homeostasis, and supporting the neurovascular unit. EEAT2 declines in patients with mild cognitive impairment (MCI), preceding Alzheimer's disease (AD) pathology and cortical hypoperfusion. Our previous work showed that GLT-1 expression is restored by blocking Calcineurin (CN)/NFAT activity while also restoring cerebral perfusion. We hypothesized that boosting astrocytic GLT-1 would preserve neurovascular coupling (NVC), markers of blood-brain barrier (BBB) integrity, and astrocyte Ca²⁺ network dynamics despite increasing amyloid- β (A β) burden.

Methods: Young 5xFAD and littermate control mice received either stereotaxic injections of AAV2/5-GFA2-GLT1 or AAV2/5-GFA2-Luciferase into hippocampus, or retro orbital injection of vectors on PHP.eB serotype. 5 months later, cranial windows were implanted on mice along with injection of GFA104-jGCAMP8f, and imaged awake 4 weeks later using two-photon microscopy. Vascular and astrocyte activity was stimulated by air puff stimulation, and activity segmented and analyzed using our previously described STONE-LAVA algorithms. Brain tissue was harvested, fixed, and labeled for markers of blood brain barrier integrity, astrocyte reactivity, and A β deposition.

Results: 5xFAD mice had significant impairments in functional activity such as neurovascular coupling, astrocytic Ca²⁺ signaling properties, and network synchronicity. We next investigated the impact of AAV expression of GLT-1 on these functional deficits. Harvested tissue was labeled for the localization of BBB proteins such as DP71, Aquaporin 4 (AQP4), and proteins related to AD pathogenesis such as GFAP and A β .

Conclusion: Functional and histological outcomes from GLT-1 downregulation in cortical astrocytes may implicate GLT-1 loss as a driver of astrocyte-vascular dysfunction. Targeting astrocytic glutamate transport may offer a therapeutic strategy for vascular and metabolic impairments observed in AD.

Disclosures: B.E. Weiss: None. J. Gollihue: None. E.B. Rucker: None. C.B. Rogers: None. J.C. Gant: None. S.D. Kraner: None. C.M. Norris: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.02/C10

Topic: B.09. Glial Mechanisms

Support: R01NS128094
R00NS105915
K99NS105915
F31NS129372
R35 NS097303
R01 NS123532
R01MH128866

Title: Lesion-remote astrocytes govern microglia-mediated white matter repair

Authors: S. MCCALLUM¹, K. B. SURESH¹, T. ISLAM¹, M. K. TRIPATHI¹, P. MANCHANDA², C. BEVERIDGE², C. RANDOLPH², R. DUTTA³, R. KAWAGUCHI⁴, G. P. MEARES⁵, G. CHOPRA², *J. E. BURDA¹;

¹Cedars-Sinai Med. Ctr., Los Angeles, CA; ²Purdue Univ., West Lafayette, IN; ³Lerner Res. Inst., Cleveland Clin., Cleveland, OH; ⁴Univ. of California Los Angeles, Los Angeles, CA; ⁵The Ohio State Univ., Columbus, OH

Abstract: Spared regions of the damaged central nervous system (CNS) undergo dynamic remodeling and exhibit a remarkable potential for therapeutic exploitation. Here, lesion-remote astrocytes (LRAs), which interact with viable neurons and glia, undergo reactive transformations whose molecular and functional properties are poorly understood. Using multiple transcriptional profiling methods, we interrogated LRAs from spared regions of mouse spinal cord following traumatic spinal cord injury (SCI). We show that LRAs acquire a spectrum of molecularly distinct, neuroanatomically restricted reactivity states that evolve after SCI. We identify transcriptionally unique reactive LRAs in degenerating white matter that direct the specification and function of local microglia that clear lipid-rich myelin debris to promote tissue repair. Fueling this LRA functional adaptation is CCN1, a secreted matricellular protein. Loss of astrocyte-derived CCN1 drives excessive, aberrant activation of local microglia, characterized by (i) abnormal molecular specification, (ii) impaired debris processing reflected by the intracellular accumulation of myelin and axon debris, and (iii) dysregulated lipid metabolism with distinctive attenuation in lipid droplet accumulation. Mechanistically, we find that CCN1 binds microglial SDC4 to augment lipid storage, linking this signaling axis to a vital repair-associated lipid buffering response in debris-clearing microglia. Accordingly, microglial deficits resulting from astrocyte CCN1 depletion culminate in blunted white matter debris clearance and impaired neurological recovery from SCI. *Ccn1*-expressing white matter astrocytes are specifically induced by local myelin damage and generated in diverse demyelinating disorders in mouse and human, pointing to their fundamental, evolutionarily conserved role in white matter repair. Our findings show that context-specific cues shape regionally distinct LRA reactivity states with functional adaptations that orchestrate multicellular processes underlying neural repair and influence disease outcome.

Disclosures: S. McCallum: None. K.B. Suresh: None. T. Islam: None. M.K. Tripathi: None. P. Manchanda: None. C. Beveridge: None. C. Randolph: None. R. Dutta: None. R. Kawaguchi: None. G.P. Meares: None. G. Chopra: None. J.E. Burda: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.03/C11

Topic: B.09. Glial Mechanisms

Support: P01 AG078116
R01 AG027297

Title: Dynamic lactate fluctuations in awake vs anesthetized animals as a function of glutamate transporter status and amyloid pathology phenotype

Authors: *J. GOLLIHUE¹, J. C. GANT², S. D. KRANER³, F. POMERLEAU⁵, G. A. GERHARDT³, C. M. NORRIS⁴;

²Sanders-Brown Ctr. on Aging Pharmacol. and Nutritional Sci., ¹Univ. of Kentucky, Lexington, KY; ³Univ. of Kentucky, Lexington, KY; ⁴Sanders-Brown Ctr. on Aging, Univ. of Kentucky, Lexington, KY; ⁵Quanteon, LLC, Nicholasville, KY.

Abstract: Hypometabolism is a prominent pathological hallmark in Alzheimer's Disease (AD) that begins before amyloid plaque or tau tangle formation and does not appear to be contingent on neuronal death. Interestingly, a surge in reactive astrocytes is observed concurrently in this earliest phase of disease progression, and a decline in astrocyte function correlates with hypometabolism, indicating a link between astrocyte function and neuronal energy consumption. In mouse models and human cases of AD, the astrocyte-specific glutamate transporter EAAT2 (Glt1a in rodents) is profoundly decreased. One crucial function of EAAT2 is its role in the lactate shuttle- a process by which astrocytes sense neuronal energy demands and provide the key metabolic substrate lactate to neurons. We hypothesized that decreased glutamate transporters on astrocytes results in decreased lactate release and supplementation to neighboring neurons, and thus the hallmark hypometabolism of neurons evident in disease. Our lab has shown that there is a significant decrease in glutamate transporters (Glt1a) in the 5XFAD mouse model of AD compared to wild type littermates. Importantly, we can overcome this deficit in 5XFAD mice using AAV-Gfa2 vectors to overexpress Glt1a specifically in astrocytes in key brain structures like the hippocampus. Next, we showed, in real time, using high-fidelity metabolite-sensing electrodes that the overexpression of Glt1a resulted in increased extracellular glutamate clearance efficiency with overexpression. One pivotal development within this study is the creation of a head-mounted platform for recording. A special headmount is affixed to the mouse skull, and a flexible window is installed over the craniotomy site. The mouse is restrained by the headmount and the MEA electrode is then inserted into the cranial window site. With this, the animal has free movement of the limbs, but can have the electrode remain in place during

awake recordings to chart fluxes in extracellular metabolites. An interesting phenomenon we first observed was that the basal extracellular lactate levels change with anesthesia; when animals are placed under isoflurane, extracellular lactate is increased compared to baseline extracellular lactate levels when fully awake. Further, we explored whether increasing astrocytic glutamate transporter expression normalizes lactate release in the context of pathology. After injection of glutamate into the hippocampus, we measured extracellular lactate in both wild type and 5XFAD mice to characterize both release and clearance dynamics relative to amyloid pathology.

Disclosures: J. Gollihue: None. J.C. Gant: None. C.M. Norris: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.04/C12

Topic: B.09. Glial Mechanisms

Support: Greater Bay Area Joint PhD Training Scheme

Title: Extracellular lactate from astrocytes, but not oligodendrocytes, supports mouse optic nerve axons during ischemia

Authors: *J. Y. T. POON, B. R. RANSOM;

The Gerald Choa Neurosci. Inst., The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Lactate has been implicated as an important metabolite supporting axons following periods of aglycemia or ischemic injury. Astrocytes convert glycogen stores into lactate for transport into axons via monocarboxylate transporters (MCTs) in response to metabolic stress. MCT1 predominantly localizes to oligodendrocytes and MCT4 to astrocytes. MCT2 is found in neurons, but also in microglia and endothelial cells. We have previously shown that increases in $[K^+]_o$ depolarize astrocytes and activate a chain of events initiating astrocytic glycogen breakdown. In circumstances where glucose is insufficient, lactate derived from astrocytic glycogen is released into the extracellular space via MCT4, providing an alternative fuel source for axons by MCT2 uptake. However, recent studies have proposed that lactate release via oligodendrocyte MCT1 is critical for the long-term support of axons. We sought to determine if lactate release seen during an acute 45-minute period of oxygen-glucose deprivation had any contribution from oligodendrocytes. The effects of pharmacological blockade of MCT1 or MCT2 on axon function were evaluated in the adult mouse optic nerve (MON), a CNS white matter preparation. Changes in the normalized compound action potential (CAP), which measured the number of functional axons within this white matter tract, were used to evaluate axon recovery. MCT2 was blocked using the non-specific inhibitor α -cyano-4-hydroxycinnamate (4-CIN), while MCT1 was blocked using the MCT1-specific inhibitor AZD3965. MONs treated with 4-CIN (mean $9.79 \pm \text{SEM } 5.00\%$) had a significantly lower normalized CAP recovery

compared to control MONs ($58.7 \pm 2.93\%$) ($P < 0.0001$, ANOVA with Tukey's post-hoc test, $n = 3-4$). In contrast, MONs treated with AZD3965 had no significant effect compared to control MONs ($58.7 \pm 2.93\%$) ($P = 0.8027$, ANOVA with Tukey's post-hoc test, $n = 4$). Furthermore, MONs treated with 4-CIN ($9.79 \pm 5.00\%$) had a significantly lower CAP recovery compared to MONs treated with AZD3965 ($60.9 \pm 1.74\%$) ($P < 0.05$, ANOVA with Tukey's post-hoc test, $n = 3-4$). Together, these findings support the idea that oligodendrocyte monocarboxylate transport does not participate in optic nerve myelinated axon protection from 45 minutes of ischemia, suggesting that oligodendrocytes are not critical for metabolic axonal support during acute ischemia. This implies that astrocytes are the primary glia cells providing lactate export under these circumstances.

Disclosures: J.Y.T. Poon: None. B.R. Ransom: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.05/C13

Topic: B.09. Glial Mechanisms

Support: P01 AG078116
R01 AG027297

Title: Targeting Astrocytic NFAT Signaling to Investigate Tau-Related Pathology in a Mouse Model of Tauopathy

Authors: *K. ZULUAGA OSORIO¹, E. B. RUCKER, III², J. GOLLIHUE³, S. D. KRANER⁴, C. B. ROGERS⁵, J. HUNT⁹, S. L. MACAULEY⁶, M.-L. B. SELENICA⁷, D. C. LEE⁸, C. M. NORRIS⁵;

¹Neurosci., ²Dept. of Pharmacol. and Nutritional Sci., ³Sanders Brown Ctr. on Aging, ⁵Sanders-Brown Ctr. on Aging, ⁶Physiol., ⁷MPP, ⁸Sanders-Brown Ctr. on Aging/ Dept. Neurosci., ⁴Univ. of Kentucky, Lexington, KY; ⁹Univ. of Kentucky, Sanders Brown Ctr. on Aging, Lexington, KY

Abstract: Tauopathies, including Alzheimer's disease and related dementias (ADRDs), are defined by the pathological accumulation of tau protein into neurofibrillary tangles (NFTs), leading to neuronal dysfunction and cognitive decline. While neuronal mechanisms have been extensively studied, emerging evidence highlights astrocytes as active contributors to disease progression. Clinical biomarker studies suggest that astrocyte reactivity can precede and predict early tau phosphorylation, raising the possibility that astrocytes play a causal role in the initiation of tau pathology. However, direct experimental testing of this hypothesis has been limited. Astrocyte reactivity can be triggered by multiple signaling cascades, one of which involves the calcium/calmodulin-dependent phosphatase calcineurin and its downstream transcription factor NFAT (nuclear factor of activated T cells). In neurodegenerative conditions, aberrant activation of the calcineurin/NFAT pathway promotes a maladaptive astrocytic phenotype characterized by

glutamate dysregulation, synaptic impairment, and chronic inflammation. Notably, inhibition of this pathway has been shown to confer neuroprotective effects in models of brain injury and neurodegeneration. To directly evaluate the role of astrocyte reactivity in tau pathology, we selectively inhibit astrocytic NFAT signaling in PS19 mice—a well-established tauopathy model—via intrahippocampal injection of adeno-associated viral (AAV) vectors expressing the NFAT-inhibitory peptide VIVIT under the astrocyte-specific Gfa2 promoter. This AAV-based approach allows for targeted modulation of astrocyte reactivity *in vivo*. To assess the consequences of astrocytic NFAT inhibition across key domains of tauopathy we use a combination of *ex vivo* electrophysiology, biochemical assays, immunohistochemistry, and immunofluorescence. These methods enable evaluation of tau hyperphosphorylation, neuroinflammatory marker expression, and synaptic dysfunction following astrocyte-targeted intervention and allows us to characterize effects of astrocyte reactivity on tau neuropathy.

Disclosures: K. Zuluaga Osorio: None. E.B. Rucker: None. J. Gollihue: None. S.D. Kraner: None. C.B. Rogers: None. J. Hunt: None. S.L. Macauley: None. M.B. Selenica: None. D.C. Lee: None. C.M. Norris: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.06/C14

Topic: B.09. Glial Mechanisms

Support: IBS-R001-D2

Title: The role of polyamine acetyltransferase (PAT/SAT1) in astrocytic GABA synthesis and tone in Alzheimer's disease

Authors: *J. LIM^{1,2}, K. KIM¹, T. LEE¹, J. JOO^{1,2}, M. BHALLA¹, M. PARK¹, M.-J. KIM¹, V. J. DREW¹, W. KOH¹, C. LEE^{1,2};

¹Inst. for Basic Sci., Daejeon, Korea, Republic of; ²Univ. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Astrocytic synthesis of γ -aminobutyric acid (GABA) plays a pivotal role in regulating brain function and pathophysiology, particularly in neurodegenerative disorders such as Alzheimer's disease (AD). In astrocytes, GABA synthesis is coupled to the degradation of putrescine. While most enzymes in the putrescine-to-GABA pathway have been identified, the enzyme initiating the metabolic cascade has remained elusive. Here, we identify polyamine acetyltransferase (PAT), also known as spermidine/spermine *N*¹-acetyltransferase 1 (SAT1), as the key enzyme catalyzing the conversion of putrescine to *N*¹-acetylputrescine, the substrate for monoamine oxidase B (MAO-B). Knockdown of PAT/SAT1 in astrocytes markedly reduced GABA synthesis and release *in vitro* and suppressed tonic GABA currents induced by putrescine incubation in *ex vivo* mouse hippocampal slices. To further dissect the underlying mechanism,

we used whole-cell patch-clamp recordings combined with direct infusion of metabolites and inhibitors. Through this approach, we demonstrated that both pharmacological and genetic inhibition of PAT/SAT1 reduced tonic GABA currents induced by putrescine infusion, and that co-application *N*¹-acetylputrescine reversed the effect of PAT/SAT1. We further demonstrate that overexpression of ornithine decarboxylase 1 (ODC1) in hippocampal dentate gyrus astrocytes elevated putrescine levels, enhanced GABA synthesis, and impaired cognitive performance, and that these effects were reversed by PAT/SAT1 inhibition. Finally, PAT/SAT1 inhibition ameliorated cognitive deficits and reduced tonic GABA inhibition in a mouse model of AD (APP/PS1). These findings identify PAT/SAT1 as a critical regulator of astrocytic GABA synthesis and highlight its potential as a therapeutic target in Alzheimer's disease.

Disclosures: J. Lim: None. K. Kim: None. T. Lee: None. J. Joo: None. M. Bhalla: None. M. Park: None. M. Kim: None. V.J. Drew: None. W. Koh: None. C. Lee: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.07/C15

Topic: B.09. Glial Mechanisms

Title: Apoe4 astrocyte transcriptomic changes during oligomeric amyloid beta clearance

Authors: *L. QIAN¹, T. TCW¹, A. M. ARRANZ², J. TCW¹;

¹Boston Univ., Boston, MA; ²Achucarro Basque Ctr. For Neurosci., Leioa, Spain

Abstract: Apolipoprotein E is a lipid transporter primarily produced by astrocytes in the brain. *APOE* allele $\epsilon 4$ (*APOE4*) increases glial reactivity, lipid dysregulation, and synaptic loss in Alzheimer's disease (AD). However, the molecular mechanism underlying *APOE4*-altered astrocyte function remains unclear. In this study, we investigated the impact of *APOE4* on astrocyte response to oligomeric amyloid beta (oA β). We generated human induced pluripotent stem cells (hiPSCs) from age-matched and sex-balanced AD patients and created isogenic *APOE* hiPSC pairs using CRISPR genome-editing. The isogenic hiPSCs were differentiated to astrocytes and challenged with 1 μ g/ml HiLyte 488-labeled oA β . A pulse-chase study was designed to elucidate the dynamics of oA β clearance, encompassing an uptake phase followed by a degradation phase. Phagocytosis and endo-lysosomal degradation were measured at phagocytic saturation (24 hr) and degradation (D24 hr) endpoints using intracellular HiLyte 488 intensity and DQ-Red BSA treatment. Our findings of reduced phagocytosis and increased intracellular retention of oA β , along with decreased DQ-Red BSA in *APOE4* astrocytes, indicated *APOE4*-driven compromises in astrocytic phagocytosis and proteasomal degradation, which primed amyloid accumulation and the buildup of AD pathology. We next applied bulk RNA sequencing to identify transcriptomic changes associated with the dynamics of oA β clearance. We identified increased cholesterol synthesis and decreased translation in *APOE4* astrocytes at baseline using pathway enrichment analysis (fGSEA) (FDR<0.01). At phagocytic saturation, *APOE4*

upregulated matrisome and stress-induced translation and downregulated phagocytosis. During degradation, *APOE4* further elevated collagen biosynthesis (core matrisome) but decreased proteasomal degradation. Through analyzing astrocyte subtypes, we found *APOE4*-specific enrichment of disease-associated astrocytes and reactive astrocytes throughout $\alpha\beta$ clearance. We also noted the increased presence of neuroinflammation-associated astrocytes specific to $\alpha\beta$ phagocytosis and lipid-accumulating reactive astrocytes in *APOE4*. Additionally, the integration of module-trait analysis (WGCNA) and transcription factor enrichment identified key transcription factors, including CTCF, ZBTB14, EGR2, and ZNF263, that mediated $\alpha\beta$ -induced aberrant epigenetic changes in *APOE4* astrocytes. These results highlighted the matrisome as an *APOE4*-specific pathological signature that intensified during $\alpha\beta$ clearance and identified epigenetic modulators as potential biomarkers or targets for AD therapeutics.

Disclosures: L. Qian: None. T. Tew: None. A.M. Arranz: None. J. Tew: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.08/C16

Topic: B.09. Glial Mechanisms

Title: Dissecting the role of astrocytes in the pathogenesis of hereditary spastic paraplegia type 11

Authors: *M. VIJAYARAGHAVAN¹, G. THAKUR², Z. CHEN³, X.-J. LI⁴;

¹Univ. of Illinois, Col. of Med., Rockford, IL; ²Univ. of Illinois, Chicago, Rockford, IL; ³Univ. of Illinois at Chicago, Rockford, IL; ⁴Dept. of Biomed. Sci., Univ. of Illinois, Rockford, IL

Abstract: Hereditary Spastic Paraplegia type 11 (HSP11) is a neurodegenerative disorder marked by progressive lower limb spasticity and weakness. It is caused by biallelic loss-of-function mutations in the *SPG11* gene, which encodes spatacsin. Spatacsin is essential for lysosomal function and cholesterol trafficking, and its absence impairs cholesterol transport and lysosomal integrity. Astrocytes play a key role in maintaining lipid homeostasis in the brain. In addition to metabolic functions, astrocytes also regulate neuroinflammation. So, under disease conditions, they undergo reactive astrogliosis, amplifying inflammatory signaling and disrupting their metabolic functions. This study investigates how *SPG11* mutations impact neuroinflammation and cholesterol trafficking, particularly in the context of APOE deficiency. We hypothesize that *SPG11*-deficient astrocytes, when stimulated with PIC, will exhibit an enhanced neuroinflammatory phenotype, evidenced by increased NF κ B activation, pro-inflammatory cytokines, and reduced APOE levels. Furthermore, we propose that treatment with the LXR agonist RGX104 will effectively reduce this neuroinflammation and ultimately lessen the neurodegenerative consequences observed in HSP11. To model *SPG11 in vitro*, astrocytes were derived from patient-specific pluripotent stem cells and characterized via qPCR and immunocytochemistry. After stimulation with PIC, the NF κ B pathway proteins and APOE were

analyzed by western blot, and cytokine secretion was assessed using ELISA. RGX104 treatment was then evaluated for its effects on protein expression and inflammation. SPG11-deficient astrocytes showed increased secretion of IL6 and TNF α , reduced IL10, elevated NF κ B pathway proteins, and reduced APOE levels compared to controls following stimulation with PIC. Treatment with RGX104 led to reduced cytokine release, suppression of NF κ B proteins, and restoration of APOE expression, indicating its potential to correct astrocytic dysfunction and reduce neuroinflammation. These findings underscore the dual role of astrocytes in lipid regulation and inflammation in SPG11 pathology and support the therapeutic potential of targeting these pathways. Future studies will explore the underlying mechanisms and assess therapeutic efficacy using preclinical animal and 3D-printed models.

Disclosures: M. Vijayaraghavan: None. G. Thakur: None. Z. Chen: None. X. Li: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.09/C17

Topic: B.09. Glial Mechanisms

Support: NIH Grant 5T32AG044402-07
Robert Packard Center Grant
NIH Grant 1R21NS125861-01

Title: Contribution of astrocytic Sparc11 to cortical synaptic dysfunction in C9orf72-FTD/ALS

Authors: *R. A. CULIBRK¹, L. M. BUSTOS¹, L. M. GITTINGS¹, B. ONDATJE¹, D. JULIAN¹, N. P. HANSEN², R. SHARMA², P. PIRROTTE², J. ANTONE³, R. G. SATTLER¹;
¹Translational Neurosci., Barrow Neurolog. Inst., Phoenix, AZ; ²Cancer and Cell Biol. Div.,
³Neurogenomics Div., The Translational Genomics Res. Inst., Phoenix, AZ

Abstract: Background. In neurodegenerative conditions, astrocytes profoundly influence neuronal viability and are key contributors to synaptic dysfunction. Recent work indicates that astrocytes regulate synapse formation, maturation, and maintenance through direct neuron contact and the release of secreted factors. Our preliminary findings reveal that the expression of Sparc11/Hevin - one such astrocyte secreted synaptogenic factor - is markedly reduced at the mRNA and protein levels in C9orf72-FTD/ALS (C9) iPSC-derived cortical astrocytes and in postmortem frontal cortex tissues from C9 patients, respectively. Here, we systematically assess the impact of Sparc11 modulation on neuronal electrophysiology and the synaptic proteome in human cortical neuron monoculture and neuron-astrocyte coculture systems.

Methods. Day 3 i³Neuron progenitor cells (9×10⁴/well), with or without human primary cortical astrocytes (hAstros; 4.5×10⁴/well), were spot-seeded into 48-well multielectrode array plates (n = 6-7) or plated on chamber slides. Astrocytes were pretreated with 5 nM SPARCL1 or control siRNA for 24 hours before coculture. Neuron monocultures received 80 nM recombinant human

Sparcl1 (rhSparcl1) continuously during biweekly medium changes. On Day 21, normalized mean firing rate (nMFR) was assessed using the Axion® Maestro system, and synaptosomes were harvested for proteomic analysis.

Results. Day 21 i³Neurons exhibit increased nMFR when cocultured with hAstros (~4.2-fold, $p < 0.05$), underscoring the role of astrocyte-derived cues in promoting excitatory synapse formation. Continuous 80 nM rhSparcl1 exposure similarly enhanced firing in i³Neuron monocultures (~3.9-fold, $p < 0.05$), suggesting Sparcl1 is sufficient to drive activity-dependent excitatory synaptic maturation without direct astrocytic contact. Conversely, siRNA-mediated depletion of astrocytic *SPARCL1* reduced the significant increase in firing attained with non-coding control siRNA-treated astrocyte coculture (~10-fold, $p < 0.01$), implicating Sparcl1 as a critical astrocyte-derived effector of synaptic potentiation.

Conclusion. These findings support a critical role for astrocytic Sparcl1 in excitatory synaptic development and maintenance and conversely suggest that its loss in C9 may contribute to cortical synaptic dysfunction and neuron death.

Disclosures: R.A. Culibrk: None. L.M. Bustos: None. L.M. Gittings: None. B. Ondatje: None. D. Julian: None. N.P. Hansen: None. R. Sharma: None. P. Pirrotte: None. J. Antone: None. R.G. Sattler: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.10/C18

Topic: B.09. Glial Mechanisms

Support: Louisiana Board of Regents Support Fund
UL Lafayette ADVANCE Minigrant, The Student Center for Research, Creativity and Scholarship
Lafayette Parish Medical Society Endowed Professorship
UL Graduate Student Organization

Title: Transcriptomic and protein analysis of the amygdala in non-human primates, *Macaca mulatta*, with self injurious behaviors

Authors: *J. BARUA¹, R. KARIYAWASAM², M. JACKSON⁴, B. L. FORET⁵, E. ROMERO³, T. SUPTY²;

¹Univ. of Louisiana, Lafayette, LA; ²Univ. of Louisiana at Lafayette, Lafayette, LA; ³NIRC, Univ. of Louisiana at Lafayette, New Iberia, LA; ⁴Biol., Univ. of Louisiana At Lafayette, Lafayette, LA; ⁵Univ. of Louisiana At Lafayette, New Orleans, LA

Abstract: Self-injurious behavior (SIB), also known as Non-suicidal Self-Injury (NSSI), is a pressing global concern where individuals intentionally harm their own bodies with no intention of committing suicide. However, NSSI is a risk factor for future suicide attempt. It is estimated

that it affects 1-4% of adults in a year, with an approximate 6% lifetime prevalence. Individuals with Autism Spectrum Disorder (ASD) and other neuropsychiatric conditions have a higher prevalence of SIB compared with the general population. SIB affects both humans and non-human primates (NHP), and is performed in response to emotional distress. Previous studies in our lab demonstrated that SIB monkeys had reduced levels of mu opioid receptors (MOR, OPRM1 gene) mRNA in the amygdala and decreased prodynorphin (PDYN) mRNA in the hypothalamus in comparison to control NHP. In a new cohort of NHPs collected for immunohistochemistry, we are examining dopamine transporter levels in the ventral tegmental area (VTA). Furthermore, RNA sequencing of the amygdala from nine male rhesus macaques (*Macaca mulatta*) with SIB and three age and sex matched controls was performed. RNAseq analysis revealed 26 differentially expressed genes (DEG) that had log2 fold changes with adjusted p values of ≤ 0.05 . We used DAVID and PANTHER to further analyze the gene pathways, some of which are connected to glial cells and stress related pathways. The astrocytic marker, Vimentin (VIM), and genes related to brain inflammation and stress including HSD11B1 (11 β -hydroxysteroid dehydrogenase type 1), CD44 (P-glycoprotein 1), RARRES2 (Chemerin), MB (Myoglobin), MIR675 (MicroRNA 675), and HBA1 (hemoglobin subunit alpha 1) were differentially expressed. Immunohistochemistry of Vimentin in the brains of five different SIB macaques and three healthy macaques without SIB were examined. We found soma cell size to be increased in Vimentin expressing glia in the prefrontal cortex, but not the amygdala. Western Blot analysis to determine protein expression levels for Vimentin, RARRES2, CD44, HSD11B1 and Caveolin-1 in the amygdala was also performed. Our studies elucidate potential mechanisms contributing to self injurious behaviors.

Disclosures: J. Barua: None. R. Kariyawasam: None. M. Jackson: None. B.L. Foret: None. E. Romero: None. T. Supty: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.11/C19

Topic: B.09. Glial Mechanisms

Support: NIH 5R01NS124037
NIH 1R01NS082413
NIH T32NS095775

Title: Understanding the roles for CD38 in astrocyte-neuronal crosstalk: implications for Parkinson's disease and circadian regulation

Authors: *A. COLAFRANCESCO¹, M. S. SIMMONS², M. L. OLSEN⁴, R. M. COWELL⁵, K. L. GAMBLE³;

¹UAB Neurosci. Grad. Programs, BIRMINGHAM, AL; ²Neurol., ³Psychiatry, Univ. of Alabama

at Birmingham, Birmingham, AL; ⁴Virginia Tech., Blacksburg, VA; ⁵Neurol., Univ. Alabama at Birmingham, Birmingham, AL

Abstract: Converging evidence implicates homeostasis of brain metabolism as an important factor in the initiation of age-related diseases, like Parkinson's Disease (PD) and Alzheimer's Disease (AD), but little is known about how different cell types of the brain contribute to the metabolic alterations seen in diseased states. Compelling studies suggest that astrocytes are responsible for maintaining the energy balance for neurons in their local environment through energetic coupling, and that circadian rhythms directly affect the bioavailability of energy metabolites. Using a bioinformatics approach, we identified PD-linked single nucleotide polymorphisms (SNPs) in the glial-enriched gene *CD38*, where homozygous carriers of the risk allele exhibit a 50% reduction in *CD38* mRNA throughout the brain. With *CD38* being responsible for 90% of nicotinamide adenine dinucleotide (NAD⁺) conversion, we propose that the *CD38*-linked increase in PD risk is due to impairments in astrocyte-derived provision of metabolic substrates to neurons and disrupted rhythmicity of the molecular clock and NAD⁺ metabolism in astrocytes. Supporting this, we identified *CD38* as a key regulator for NAD⁺ balance, where *Cd38*^{-/-} mice have elevated NAD⁺/NAM levels and a robust increase in PAR-modified proteins suggesting a dysregulation of energy homeostasis. RNA sequencing of astrocytes isolated from the midbrain of adult *Cd38*^{-/-} mice also revealed decreased expression of genes involved in oxidative phosphorylation and senescence, and an increase in pro-inflammatory, glycogen metabolism, and regulatory clock genes. To investigate the functional consequences of *CD38* deficiency on astrocytic state *in vivo*, we performed immunofluorescence for markers of astrocytic reactivity (GFAP, S100 β), and found increased astrocytic reactivity in the substantia nigra of *Cd38*^{-/-} mice, suggesting that *CD38* may play a larger role in the phenotypic states of astrocytes. Beyond its role in astrocytic state, we wanted to examine the role of *CD38* in molecular clock disruption. We treated organotypic cultures of the substantia nigra isolated from PER2Luc^{+/+} transgenic mice with a *CD38* Inhibitor, MK-0159 (1 μ M; MCE, Cat. No.: HY-150508) and found that *CD38* inhibition increased the PER2::LUC period length, suggesting that elevated NAD⁺ may slow the molecular clock cycle. Together, these findings position *CD38* as a key regulator of astrocyte metabolism and circadian function, offering new insight into how metabolic disruption in glial cells may drive vulnerability to neurodegenerative diseases like Parkinson's Disease.

Disclosures: A. Colafrancesco: None. M.S. Simmons: None. M.L. Olsen: None. R.M. Cowell: None. K.L. Gamble: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.12/C20

Topic: B.09. Glial Mechanisms

Support: American Heart Association 24PRE1198593

Title: Astrocytic Chrdl1 reduces hippocampal neuronal death via GluA2-AMPA stabilization under ischemic conditions

Authors: *B. R. BOYLE¹, A. J. GLEICHMAN², S. CARMICHAEL³, E. BLANCO SUAREZ¹; ¹Neurosci., Thomas Jefferson Univ., Philadelphia, PA; ²Neurolog. Surgery, The Ohio State Univ. Col. of Med., Columbus, OH; ³Neurol., UCLA Sch. Med., Los Angeles, CA

Abstract: Chordin-like 1 (Chrdl1) is an astrocytic protein that stabilizes GluA2-containing AMPA receptors (GluA2-AMPA) at synapses and is expressed heterogeneously across different brain regions. GluA2-AMPA play crucial roles in calcium homeostasis, which is vital for learning and memory processes. After excitotoxic events like ischemic stroke, GluA2-AMPA decrease at hippocampal synapses, heightening neuronal vulnerability to excitotoxicity. We hypothesize that increasing astrocytic Chrdl1 will stabilize GluA2-AMPA at hippocampal synapses, protecting neurons from excitotoxicity-induced cell death. To test this, we used *in vitro* (oxygen/glucose deprivation, OGD) and *in vivo* (photothrombosis, PT) models to induce ischemic conditions, known to trigger excitotoxicity. Immunocytochemistry in primary hippocampal neuronal cultures was employed to assess surface and internalized GluA2 levels, comparing neurons treated with or without Chrdl1 prior to OGD and those under normoxic conditions. *In vivo*, we transduced Chrdl1 in astrocytes via AAV.PHP-eB, induced focal ischemic stroke using PT in the mouse hippocampus, and analyzed GluA2 levels post-PT by immunohistochemistry around the injury site. To evaluate cell death *in vitro*, we used a lactate dehydrogenase release assay for cytotoxicity levels and assessed cleaved-caspase3 in hippocampal neurons immediately after OGD and 72 hours later for delayed cell death. *In vivo*, we co-stained NeuN with TUNEL using immunohistochemistry. Lastly, we evaluated the cognitive outcomes in Chrdl1 transduced mice compared to control after hippocampal PT via Novel Object Recognition test and Barnes maze. Our findings demonstrate that Chrdl1 treatment or overexpression before OGD or hippocampal PT prevents GluA2-AMPA internalization, enhancing hippocampal neuron viability. This data highlights Chrdl1's role in stabilizing GluA2-AMPA in vulnerable hippocampal neurons after excitotoxicity induced by ischemic conditions, suggesting that astrocytic Chrdl1 could serve as a novel 'resilience factor', preventing neuronal death in early phases after ischemia, and potentially improving cognitive performance later.

Disclosures: B.R. Boyle: None. A.J. Gleichman: None. S. Carmichael: None. E. Blanco Suarez: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.13/C21

Topic: B.09. Glial Mechanisms

Support: RS-2025-00562132
RS-2023-00262810

Title: Stim1 modulation in astrocytes as a therapeutic target for acute ischemic stroke

Authors: *S. CHOI¹, S. HYUN², S. KIM³;

¹Kyung Hee Univ., Seoul, Korea, Republic of; ²KHU-KIST Dept. of Converging Sci. and Technology, Kyunghee Univ., seoul, Korea, Republic of; ³Dept. of Physiol., Kyung Hee Univ. Col. of Korean Med., Seoul, Korea, Republic of

Abstract: Astrocytes critically influence ischemic stroke outcomes through calcium signaling-dependent mechanisms, which can be both beneficial and detrimental. Stromal interaction molecule 1 (STIM1), a key regulator of store-operated calcium entry, has emerged as an essential mediator of intracellular calcium dynamics in astrocytes, yet its role in acute stroke remains largely unknown. Here, we demonstrate that conditional knockout of astrocytic STIM1 in mice dramatically reduces infarct volume and improves neurological function following ischemic stroke. *In vivo* two-photon imaging revealed that astrocytic STIM1 knockout reduces the amplitude and duration of both spreading depolarization-associated and spontaneous calcium transients during acute ischemia. These transients are highly correlated with improved neurological outcomes. Further, the astrocytic STIM1 knockout mitigated excitotoxic stress by accelerating glutamate clearance and reducing total glutamate burden during ischemic stroke. Our findings establish astrocytic STIM1 as a critical regulator of calcium and glutamate dynamics during ischemic stroke, and therefore, targeting astrocytic STIM1 represents a promising therapeutic avenue for alleviating ischemic brain damage by reducing calcium overload and glutamate excitotoxicity.

Disclosures: S. Choi: None. S. Hyun: None. S. Kim: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.14/C22

Topic: B.09. Glial Mechanisms

Title: Psychedelic control of neuroimmune interactions governing fear

Authors: *E. N. CHUNG;

Sch. of Med., UCSF, San Francisco, CA

Abstract: Neuroimmune interactions—signals transmitted between immune and brain cells—regulate many aspects of tissue physiology, including responses to psychological stress, which can predispose individuals to develop neuropsychiatric diseases. Still, the interactions between haematopoietic and brain-resident cells that influence complex behaviours are poorly understood. Here, we use a combination of genomic and behavioural screens to show that

astrocytes in the amygdala limit stress-induced fear behaviour through epidermal growth factor receptor (EGFR). Mechanistically, EGFR expression in amygdala astrocytes inhibits a stress-induced, pro-inflammatory signal-transduction cascade that facilitates neuron-glia crosstalk and stress-induced fear behaviour through the orphan nuclear receptor NR2F2 in amygdala neurons. In turn, decreased EGFR signalling and fear behaviour are associated with the recruitment of meningeal monocytes during chronic stress. This set of neuroimmune interactions is therapeutically targetable through the administration of psychedelic compounds, which reversed the accumulation of monocytes in the brain meninges along with fear behaviour. Together with validation in clinical samples, these data suggest that psychedelics can be used to target neuroimmune interactions relevant to neuropsychiatric disorders and potentially other inflammatory diseases.

Disclosures: E.N. Chung: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.15/C23

Topic: B.09. Glial Mechanisms

Support: VA MERIT REVIEW AWARD I01BX001819
NIH/NIAAA U01AA029965
NIH/NIAAA R01AA029486
NIH/NIAAA P60AA010760

Title: Astrocyte reactivity in a preclinical model of alcohol dependence

Authors: J. G. HASHIMOTO^{1,2}, A. E. GONZALEZ³, H. NEDELESCU⁴, A. J. ROBERTS⁵, M. ROBERTO⁶, *M. GUIZZETTI^{7,2};

¹Behavioral Neurosciences, Oregon Hlth. & Sci. Univ., Portland, OR; ²VA Portland Hlth. Care Syst., Portland, OR; ³Translational Med., ⁴Neurosci., ⁵Animal Models Core, ⁶Dept. of Mol. Med., The Scripps Res. Inst., La Jolla, CA; ⁷OHSU, Portland, OR

Abstract: In the healthy brain, astrocytes play numerous essential roles; in response to harmful stimuli or trauma, however, these physiological roles are diminished, and astrocytes acquire neuroimmune functions to become reactive astrocytes. While reactive astrocytes under several pathological conditions have been characterized, astrocyte reactivity in preclinical models of alcohol use disorder (AUD) has not been demonstrated. The chronic intermittent ethanol-two-bottle choice (CIE-2BC) exposure model induces escalation of drinking, modeling certain aspects of AUD (i.e. alcohol dependence) and increases neuroimmune activation. To characterize the molecular alterations in astrocytes occurring in the CIE-2BC model, we used the Aldh1l1-EGFP/Rpl10a transgenic mice to isolate actively translating RNA via an eGFP tagged ribosomal protein expressed only in astrocytes. Aldh1l1-EGFP/Rpl10a mice underwent CIE-2BC to induce

alcohol dependence; control mice were exposed to air during the CIE procedure and underwent 2BC drinking between CIE exposures; an alcohol-naïve group was also included. Translating Ribosome Affinity Purification (TRAP) was carried out on brain punch dissections of medial prefrontal cortex (mPFC), amygdala (AMY), and nucleus accumbens (NAC). RNA-Seq was run on input RNA, representing the bulk tissue RNA, and TRAP-RNA. CIE-2BC significantly altered 345 genes in mPFC, 384 in AMY, and 386 in NAC in the astrocyte (TRAP) fraction. Analysis of the input RNA showed fewer genes regulated by CIE-2BC in all the brain regions; 81 in mPFC, 68 in AMY, and 108 in NAC. Comparison of the genes regulated in astrocytes showed 101 genes were regulated by CIE-2BC in all three regions with 171 genes regulated only in mPFC, 201 genes only in AMY, and 208 genes only in NAC. Gene category enrichment analysis of CIE-2BC regulated genes in astrocytes was conducted and immune function related categories were the top enriched categories in all three brain regions. In the transition to reactivity, astrocytes undergo morphological changes. We examined astrocyte-specific morphological changes by CIE-2BC in Aldh1l1-EGFP-Rpl10a mice, which enabled reliable 3D astrocyte rendering in Neurolucida software. Analysis of amygdala astrocyte 3D reconstructions revealed increased astrocyte complexity ($p=0.0285$), nodes ($p=0.0088$), convex hull volume ($p=0.0044$) and surface area ($p=0.0044$) in CIE-2BC vs naïve, but not in CIE-2BC vs 2BC, or 2BC vs naïve, suggesting that alcohol dependence alters astrocyte morphology. These findings reveal the reactive astrocyte signature of alcohol dependence important in the development of specific therapeutics.

Disclosures: J.G. Hashimoto: None. A.E. Gonzalez: None. H. Nedelescu: None. A.J. Roberts: None. M. Roberto: None. M. Guizzetti: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.16/C24

Topic: B.09. Glial Mechanisms

Support: NASA NNX15AI01H
NIH R21AA030086
VA BX005403
NSF-2242771

Title: The effects of adolescent binge ethanol exposure on astrocyte-neuronal communication at the tripartite synapse

Authors: *O. COULTER;
Marshall Univ., HUNTINGTON, WV

Abstract: Adolescence is a crucial period of neurological development. Binge-drinking during this period has been associated with long-term disruption of neuronal and cognitive function.

How non-neuronal cells contribute to these deficits remains understudied despite growing evidence that astrocytes are important regulators of neuronal function. However, the role of astrocytes in regulating more complex behaviors remains understudied. Our previous data demonstrate that adolescent intermittent ethanol (AIE) disrupts peripheral astrocyte process (PAP)-synaptic proximity in a subregion-dependent manner and impairs astrocyte function in the dorsal hippocampal (dHipp). The ensheathment and proximity of peripheral astrocyte processes (PAPs) to synapses facilitates necessary bidirectional crosstalk that occurs through the release of neuro- and glio-transmitters and astrocyte Ca^{2+} signaling.

Male Sprague Dawley rats received hippocampal intracranial injections of various adeno-associated viruses: astrocyte-specific Ca^{2+} indicator (GCaMP6f), adenosine sensor (GRAB_Ado1.0) + fiber, and hM3D(Gq). Adolescent rats received EtOH (5g/kg) or water intermittently via gavage over 16 days followed by a 26-day washout period. Rats then performed the contextual fear conditioning task with simultaneous fiber photometry recordings following clozapine-n-oxide administration. A subset of brains were prepared for immunohistochemistry, stimulated emission depletion (STED) microscopy, and slice physiology. We demonstrate that PAPs physically and functionally decouple from synapses. Moreover, astrocytes show reduced Ca^{2+} responsivity to neuronal activation in the dorsal hippocampus despite increased glutamate availability within the synaptic cleft. We show that the EtOH-induced reduction in astrocyte Ca^{2+} signaling is not due to a loss of astrocyte membrane-bound glutamatergic receptors or transporters. These changes coincide with EtOH-induced deficits in fear acquisition in the contextual fear conditioning task that are attenuated through chemogenetic recovery of astrocyte Ca^{2+} activity. We are able to demonstrate how chemogenetic astrocyte activation impacts downstream changes in gliotransmitter release and synaptic glutamate release that may be contributing to AIE-induced deficits in fear acquisition. These data emphasize a critical role for astrocyte-synaptic crosstalk in the regulation of behavior and demonstrates the potential of non-neuronal targeted treatments to improve decision-making outcomes during abstinence.

Disclosures: O. Coulter: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.17/C25

Topic: B.09. Glial Mechanisms

Support: NIH: K99NS105915
NIH: R00NS105915
American Academy of Neurology
the California Institute for Regenerative Medicine
Wings for Life
Paralyzed Veterans of America
NIH: F31NS129372

Title: Molecular dissection of astrocyte reactivity states linked to regenerative plasticity in spared tissue regions after CNS injury

Authors: *S. MCCALLUM¹, K. B. SURESH¹, A. GUHA², J. E. BURDA³;

¹Cedars Sinai Med. Ctr., Los Angeles, CA; ²electrical and computer science engineering, UCLA, Los Angeles, CA; ³Ctr. for Neural Sci. and Med., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: The injured mammalian central nervous system (CNS) exhibits a remarkable capacity for synaptic plasticity and circuit remodeling. Following spinal cord injury (SCI) intraspinal circuit reorganization in spared tissue regions neighboring a lesion can re-establish brain-cord communication, facilitating spontaneous motor recovery. The cellular and molecular mechanisms underlying this endogenous neural repair process within spared tissue regions are poorly defined. Spared neural tissue neighboring a spinal cord lesion, contains large populations of reactive astrocytes that intermingle with viable neurons and glia. The functions of reactive astrocytes in actively remodeling spared tissue are poorly understood but may regulate synapse remodeling and modulate inflammation. Understanding molecular mechanisms employed by reactive astrocytes to support neural remodeling after SCI can identify new therapeutic targets for stimulating endogenous pathways of CNS recovery. Thus, we employed a mouse model of SCI wherein circuit plasticity in spared spinal cord regions drives locomotor recovery. At various time points following SCI, single nuclei RNA-sequencing (snRNA-seq) and Visium spatial transcriptomics were used to interrogate the molecular heterogeneity of astrocytes and neighboring cell types. All major spinal cord cell types were detected and contained spatially-restricted and molecularly defined subpopulations that evolved over time in an injury-dependent manner. Signaling network propagation models were used to investigate ligand-receptor-mediated pathways of astrocyte cellular crosstalk within a local cellular niche. This approach identified spatially and temporally regulated cohorts of astrocyte-mediated intercellular signaling pathways with neurons or microglia associated with neural repair. This study lays essential groundwork for understanding the molecular and functional properties of injury-reactive astrocytes in neural tissue regions spared after CNS injury. In addition, We provide an open-access searchable resource for interrogating molecularly distinct, neuroanatomically restricted LRA reactivity states. Newly identified *candidate pathways of astrocyte intercellular signaling can serve as experimental therapeutic targets for harnessing endogenous pathways of functionally meaningful regenerative plasticity in a wide range of CNS pathology. Likewise, viable targets may be identified to attenuate maladaptive circuit remodeling underlying SCI comorbidities such as neuropathic pain and autonomic dysfunction.*

Disclosures: **S. McCallum:** A. Employment/Salary (full or part-time): Cedars Sinai Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; American Academy of Neurology, The California Institute for Regenerative Medicine. **K.B. Suresh:** A. Employment/Salary (full or part-time): Cedars Sinai Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; F31NS129372. **A. Guha:** None. **J.E. Burda:** 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.; K99NS105915, R00NS105915, Wings for Life, Paralyzed Veterans of America.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.18/C26

Topic: B.09. Glial Mechanisms

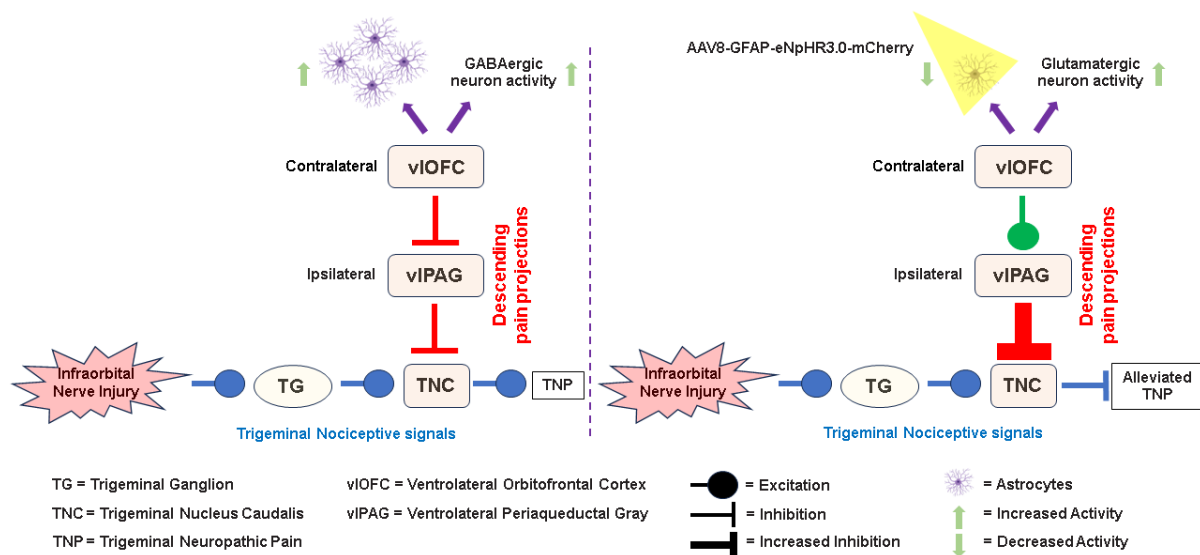
Support: NRF Grant NRF2023R1A2C1008079

Title: Optogenetic modulation of orbitofrontal cortex astrocytes alleviates trigeminal neuropathic pain via restoration of descending pain circuits

Authors: *J. ISLAM¹, M. ALI¹, Y. PARK²;

¹Col. of Medicine, Chungbuk Natl. Univ., Cheongju, Korea, Republic of; ²Neurosurg., Chungbuk Natl. Univ. Hospital, Neurosurg., Cheongju-Si, Korea, Republic of

Abstract: Trigeminal neuropathic pain (TNP) is a persistent condition marked by exaggerated nociceptive responses and neuroinflammatory processes. Although astrocytes are increasingly recognized as key modulators of pain, their contribution to descending pain regulation through the ventrolateral orbitofrontal cortex (vLOFC) remains insufficiently characterized. In this study, we examined how optogenetic modulation of vLOFC astrocytes affects pain behaviors in a chronic constriction injury model targeting the infraorbital nerve (CCI-ION) in adult female Sprague Dawley rats. Naïve and sham-operated animals served as controls. To manipulate astrocytic activity, AAV8 vectors encoding GFAP-driven ChR2, eNpHR3.0, or mCherry were injected into the vLOFC. Behavioral outcomes were evaluated using acetone, von Frey, and elevated plus maze tests. Additionally, we performed in vivo extracellular recordings from the ventrolateral periaqueductal gray (vLPAG) and ventral posteromedial (VPM) thalamus. TNP animals exhibited facial hyperalgesia, reduced vLPAG excitability, and elevated thalamic firing, which coincided with increased astrocytic activity in the vLOFC. Notably, selective inhibition of vLOFC astrocytes restored cortical glutamatergic output, enhanced vLPAG neuronal firing, and attenuated thalamic hyperactivity. This intervention also alleviated pain hypersensitivity and anxiety-like behavior, while reducing expression of neuroinflammatory markers such as P2X3 and Iba-1. Conversely, astrocytic activation and control vectors had no impact on TNP symptoms, emphasizing the functional specificity of astrocytic suppression. These results highlight the critical role of vLOFC astrocytes in modulating pain-related circuits and suggest that their targeted inhibition may represent a promising strategy for treating trigeminal neuropathic pain.



Disclosures: J. Islam: None. M. Ali: None. Y. Park: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.19/C27

Topic: B.09. Glial Mechanisms

Support: NIH R03 MH127401-01A1

Title: Astrocyte morphological remodeling and synaptic contact alterations in two genetic mouse models of Autism Spectrum Disorder

Authors: *Y. CHEN¹, J. J. KIM¹, S. DILLON¹, N. HARDING¹, T. DEEMYAD²;
²Otolaryngology - Head and Neck Surgery, ¹Johns Hopkins Univ., Baltimore, MD

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and the presence of restricted, repetitive behaviors. While neuronal mechanisms have been the primary focus of ASD research, accumulating evidence suggests that astrocytes play an essential role in shaping neural circuits and may contribute to ASD pathophysiology. In this study, we investigate astrocytic contributions to circuit dysfunction of two well-characterized, non-syndromic ASD risk genes: *SHANK3*, which encodes a synaptic scaffolding protein, and *CNTNAP2*, which encodes the cell adhesion protein CASPR2, a neurexin family member involved in axon-glia interactions and ion channel localization. To investigate the impact of these mutations on astrocyte structure and synaptic engagement, we employed immunohistochemistry, high-resolution confocal imaging, and 3D morphometric analyses of astrocytes in the somatosensory cortex. In both *SHANK3b*^{-/-} and

CNTNAP2^{-/-} mouse models, we observed changes in astrocyte morphology, including alterations in branch complexity, overall volume, and cell density, relative to wild-type (WT) controls. These structural abnormalities emerged during early postnatal periods and preceded known behavioral phenotypes, suggesting a potential role in the establishment of dysfunctional neural circuits rather than being a consequence of downstream pathology. To examine astrocyte-synapse interactions at the ultrastructural level in adulthood, we performed post-embedding immunogold electron microscopy targeting GFAP-positive astrocytes and parvalbumin-positive (PV+) interneurons. Across both models, we observed genotype-associated differences in the number and surface coverage of astrocytic processes in direct contact with presynaptic terminals. Together, these findings highlight a shared astrocytic phenotype across distinct ASD gene models and underscore the importance of astrocyte contributions to ASD-related circuit abnormalities. This work emphasizes the need to include non-neuronal mechanisms in ASD research. It also provides a foundation for future studies aimed at astrocyte-targeted therapeutic strategies.

Disclosures: Y. Chen: None. J.J. Kim: None. S. Dillon: None. N. Harding: None. T. Deemyad: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.20/C28

Topic: B.09. Glial Mechanisms

Support: NIH R03 MH127401-01A1

Title: Mutations in Shank3 and CNTNAP2 impair astrocytic calcium dynamics and synaptic associations in Autism Spectrum Disorder

Authors: *J. J. KIM¹, Y. CHEN¹, S. G. SADEGHI², T. DEEMYAD²;
²Otolaryngology - Head and Neck Surgery, ¹Johns Hopkins Univ., Baltimore, MD

Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental condition increasingly regarded as a synaptopathy, characterized by disruptions in synaptic structure, function, and plasticity that are essential for experience-dependent sensory system refinement. These processes are shaped by the coordinated interplay of distinct neural cell types, including neurons and non-neuronal glial cells such as astrocytes. The ASD risk genes Shank3 and CNTNAP2, traditionally studied for their roles in neuronal synaptic development, are also expressed in astrocytes, implicating these glial cells in ASD-related synaptic pathology. Given observed alterations in both inhibitory interneurons and astrocytes in ASD, and the critical role of astrocytes in regulating synaptic environments, their dysfunction may contribute to circuit-level abnormalities. This study investigates how Shank3 and Cntnap2 mutations affect astrocyte calcium signaling dynamics in ASD models.

To address this, we are employing In vivo two-photon calcium imaging of spontaneous astrocytic events and their response to whisker stimulation in layer 2/3 of the barrel cortex of awake adult mice. In both Shank3b^{-/-} and CNTNAP2^{-/-} mouse models, we observed changes in astrocyte function, including alterations to calcium signalling event propagation speed, area, duration, and amplitude, relative to wild-type (WT) controls. These functional abnormalities show alterations to many aspects of astrocyte signalling, suggesting a correlation between abnormal synapse function in ASD and the modulatory role astrocytes have. Furthermore, these findings suggest that Shank3 does not just have a functional effect on the post-synapse, but instead that ASD as a synaptopathy must be understood also on its effects on astrocytic function. This work indicates that astrocytic modulation of synaptic function may be disrupted in ASD models and the need to include non-neuronal mechanisms in ASD research. Circuit dynamics studies that incorporate altered modulatory astrocytes may yield more accurate models for ASD understanding. It also provides a foundation for future studies aimed at astrocyte-targeted therapeutic strategies.

Disclosures: J.J. Kim: None. Y. Chen: None. S.G. Sadeghi: None. T. Deemyad: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.21/C29

Topic: B.09. Glial Mechanisms

Support: NS129555
NS129205

Title: Modulation of inhibitory tone by Fmr1 KO astrocytes in the mouse hippocampus

Authors: *I. M. ETHELL¹, V. WAGNER², S. M. MAPLES⁴, A. NORMAN³, S. SUTLEY-KOURY⁵, M. RAIS², P. W. HICKMOTT⁶;

²Biomed. Sci., ³Div. of Biomed. Sci., ¹Univ. of California, Riverside, Riverside, CA;

⁴Psychology, Univ. of Illinois, Urbana-Champaign, Champaign, IL; ⁵Psychiatry, Stanford, Riverside, CA; ⁶Psychology & Interdepartmental Neurosci. Pgm., Univ. California, Riverside, Riverside, CA

Abstract: Fragile X syndrome (FXS) is a leading genetic cause of autism-like symptoms, including sensory hypersensitivity and circuit hyperexcitability, resulting from epigenetic silencing of the Fragile X messenger ribonucleoprotein (*Fmr1*) gene. Recent observations in humans and *Fmr1* knockout (KO) animal models of FXS suggest abnormal GABAergic signaling may underlie pathophysiology of FXS. As most studies have focused on neuronal mechanisms, the role of astrocytes in mediating abnormal inhibition in FXS is largely unknown. Previous studies have reported a reduction in the levels of GABA_A receptor expression and impaired inhibition in global *Fmr1* KO mice. Interestingly, astrocyte-specific *Fmr1* deletion

during P14-P28 period also affected number of perisomatic GABAergic synapses in CA1 hippocampus. We also observed a reduction in the expression of extrasynaptic but not synaptic GABA_A receptor subunits in conditional KO. However, while tonic GABA currents were reduced in CA1 neurons of global KO, conditional KO mice showed a trend towards increased tonic inhibition. Our results suggest that GABA transport in astrocytes may contribute to the changes in tonic inhibition. Reduced levels of GABA transporter GAT3/4 in hippocampus astrocyte-specific *Fmr1* conditional KO may lead to reduced uptake of extracellular GABA by astrocytes, explaining higher tonic GABA. Indeed, whole cell recordings further confirmed the impaired functions of GAT3/4 in KO astrocytes. While the pharmacological inhibition of GAT3 reduced tonic GABA currents in WT, no changes were observed in KO mice. Our work supports astrocytes as key players in the development and regulation of inhibitory circuits in FXS and a potential target for therapies to relieve FXS-associated phenotypes.

Disclosures: I.M. Ethell: None. V. Wagner: None. S.M. Maples: None. A. Norman: None. S. Sutley-Koury: None. M. Rais: None. P.W. Hickmott: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.22/C30

Topic: B.09. Glial Mechanisms

Support: JSPS Research Fellowship for Young Scientists (23KJ0285)

Title: Autism-associated sparcl1/hevin mutant has impacts on persistent angiogenesis via inflammatory response

Authors: *T. TAKETOMI^{1,2}, H. KIKUKAWA³, K. UEDA², T. YASUDA⁴, N. YAMASHITA³, A. HARADA⁵, M. SATO⁵, R. HARADA⁶, K. IWASAKI⁵, S. MIZUNO^{7,2}, S. TAKAHASHI^{7,2}, F. TSURUTA^{8,2};

²PhD Program in Human Biol., ³Master's Program in Biol., ⁴Doctoral Program in Biol., ⁵Life Sci. Ctr. for Survival Dynamics, Tsukuba Advanced Res. Alliance, ⁶Ctr. for Computat. Sci., ⁷Lab. Animal Resource Ctr., ⁸Fac. of Life and Envrn. Sci., ¹Univ. of Tsukuba, Tsukuba, Japan

Abstract: Autism spectrum disorder (ASD) is the most common neurodevelopmental disorder characterized by social interaction defects and repetitive behaviors. It has been reported that not only deficits in excitatory-inhibitory synaptic balance, but also persistent angiogenesis occurs in the brain of ASD patients. The ASD pathogenesis is known to be regulated by ASD-associated gene mutations. Genome-wide association studies have shown that mutations in the *Sparcl1* gene increase the risk of ASD. SPARCL1 is a secreted extracellular matrix protein that promotes synaptic connectivity and inhibits angiogenesis. Our previous study reported that a single amino acid substitution of Trp-647 to Arg (WR), which is associated with a familial case of ASD, exhibits abnormal protein structure, leading to low secretion levels *in vitro* (T Taketomi *et al.*,

Sci Rep, 2022). However, the mechanism linking the ASD-associated single amino acid substitution in SPARCL1 to ASD pathogenesis *in vivo* remains unaddressed. In this study, we investigated the effects of the *Sparcl1* WR mutation using *Sparcl1* heterozygous WR knock-in (*Sparcl1*^{WR/+}) mice. We observed a significant increase in vascular complexity in the cerebral cortex of *Sparcl1*^{WR/+} mice. Mechanistically, the SPARCL1 WR dimer interacted with Toll-like receptor 4 (TLR4) and promoted nuclear translocation of p65, indicating an inflammatory response *in vitro*. Immunohistochemical analysis further revealed SPARCL1 localization in the perivascular regions of the developing mouse cortex, while phosphorylated p65 (Ser536) was upregulated in astrocytes of *Sparcl1*^{WR/+} mice (4-week-old), suggesting neuroinflammation. To assess the impact of the WR mutation on angiogenesis, we performed qPCR analysis and confirmed the upregulation of *Vegfa* mRNA in both the cerebral cortex and primary astrocytes. Finally, we found that *Sparcl1*^{WR/+} mice (8-week-old) exhibit repetitive behavior in the marble burying test. In conclusion, we show that this single amino acid substitution triggers activation of angiogenesis, resulting in abnormal vascular wiring in the mPFC of the *Sparcl1*^{WR/+} mice. We also confirm that the *Sparcl1*^{WR/+} exhibits ASD-like behavior. These data suggest a potential link between abnormal angiogenesis and the pathogenesis of ASD.

Disclosures: T. Taketomi: None. H. Kikukawa: None. K. Ueda: None. T. Yasuda: None. N. Yamashita: None. A. Harada: None. M. Sato: None. R. Harada: None. K. Iwasaki: None. S. Mizuno: None. S. Takahashi: None. F. Tsuruta: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.23/C31

Topic: B.09. Glial Mechanisms

Support: ANR-22-CE17-0035
U19MH106434
NIH R01 MH095741

Title: Altered inflammatory response in iPSC-derived microglia and astrocytes from bipolar disorder patients

Authors: *R. SANTOS¹, F. RENARD¹, C. MARCHETTO², F. H. GAGE³;
¹Inst. of Psychiatry and Neurosci. of Paris, Paris, France; ²Univ. of California San Diego, San Diego, CA; ³LOG-G, Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Bipolar disorder (BD) is a severe and complex psychiatric condition that affects 1-3% of the population, marked by recurrent episodes of mania and depression. Growing evidence suggests glial contributions to BD pathophysiology, particularly through neuroinflammation. Numerous studies have consistently demonstrated elevated levels of pro-inflammatory cytokines in the peripheral blood and cerebrospinal fluid of individuals with BD; however, post-mortem

brain studies have produced conflicting data regarding astrocyte and microglia densities, as well as their activation states. Despite these findings, the exact mechanisms by which neuroinflammation contributes to the development and progression of BD are still poorly understood. Using induced pluripotent stem cell (iPSC)-derived microglia and astrocytes, we explored immune dysregulation as a potential driver of BD. Our results show elevated levels of pro-inflammatory cytokines in BD microglia after LPS stimulation compared to control, indicating heightened inflammatory sensitivity in BD microglia. Also microglia exhibited impaired phagocytic activity, with reduced uptake of fluorescent particles. Similarly, astrocytes derived from BD iPSCs displayed significant alterations in gene expression related to synaptic function and inflammatory pathways, as well as impaired neurotrophic support for neurons. These findings provide new insights into the role of glial dysfunction in BD, suggesting that it may contribute to both the neuroinflammatory and neurodevelopmental abnormalities observed in this disorder.

Disclosures: R. Santos: None. F. Renard: None. C. Marchetto: None. F.H. Gage: None.

Poster

PSTR009: Astrocytes: Disease Mechanisms I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR009.24/C32

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: UCLA Marion Bowen 2023
NIH Grant NS111583

Title: Consequences of molecularly defined reactive astrogliosis in vivo

Authors: *A.-S. HUANG¹, P. CHEN², V. PANDEY³, M. OLLIVIER¹, L. WU¹, J. WOHLSCHEGEL¹, R. KAWAGUCHI¹, M. CHEN⁴, B. S. KHAKH⁵;

¹Univ. of California, Los Angeles (UCLA), Los Angeles, CA; ²Physiol., UCLA David Geffen Sch. of Med., Los Angeles, CA; ³Biol. Chem., UCLA, LOS ANGELES, CA; ⁴Spinal Cord & Brain Injury Res. Ctr. (SCoBIRC), Neurosci., Univ. of Kentucky, Lexington, KY; ⁵Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Astrocytes are critical for normal brain function and undergo reactive astrogliosis manifested by morphological, cellular, and molecular changes during diverse CNS disease states that encompass neuroinflammation. Due to the inseparable co-occurrence of reactive astrogliosis with underlying diseases, it has proven challenging to understand the causal contributions of reactive astrogliosis to pathophysiology. Here, to address this shortfall, we deployed a genetic approach that induces *de novo* reactive astrogliosis independent of disease via the expression of the gene LZK (MAP3K13) in astrocytes. In adult mice, LZK expression in astrocytes of the dorsolateral striatum resulted in multidimensional changes in astrocytes characteristic of reactive astrocytes (RA), including upregulation of GFAP, hypertrophic morphology, reduced gap

junction connectivity, increased calcium signaling, and RA transcriptomic signatures. Functionally, LZK-induced reactive astrogliosis (LiRA) induced behavioral hyperactivity with increased neuronal excitability. Using astrocyte cell-surface proteomics and mapping, we found that these functional alterations were accompanied by increased interactions between LiRA astrocytes and microglia, and reduced interactions with neurons. Using brain-wide LiRA to mimic neuroinflammation without systemic effects, we found that LiRA induced inflammatory signatures in astrocytes across multiple brain regions without changing their distinct regional identities. Behaviorally, the mice developed learned helplessness and diminished nesting behaviors indicative of cognitive and psychiatric malfunction. Together, based on molecular, cellular, neural circuit and *in vivo* evaluations across biological scales, our findings reveal causal roles of reactive astrogliosis for the modulation of neural circuits and behaviors, directly demonstrating that reactive astrocytes themselves drive behavioral alterations that contribute to diverse disease states including neuroinflammation. We report unambiguous identification of the causal links between reactive astrogliosis and central nervous system dysfunctions, which may accelerate and guide the development of astrocyte-based therapies for neuroinflammation and for other brain disorders.

Disclosures: A. Huang: None. P. Chen: None. V. Pandey: None. M. Ollivier: None. L. Wu: None. J. Wohlschlegel: None. R. Kawaguchi: None. M. Chen: None. B.S. Khakh: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.01/C33

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant UG3/UH3 CA275669 (M.J.S.)
NIH Grant R01 AG071686 (M.J.S.)
NIH Grant T32 GM145408 (Y.H.)
The Robert and Arlene Kogod Center on Aging at Mayo Clinic

Title: Single-cell spatial mapping of human hippocampal brain cell senescence in cognitive decline

Authors: *Y. HA^{1,2,3}, C. M. CARVER^{4,5}, J. SHI⁶, J. M. KACHERGUS⁶, Y. LIU⁷, P. VEMURI⁸, E. THOMPSON⁶, A. T. NGUYEN⁹, M. J. SCHAFER^{4,3,5,10};

²Med. Scientist Training Program, ³Neurosci., ⁴Physiol. and Biomed. Engin., ⁵Robert and Arlene Kogod Ctr. on Aging, ¹Mayo Clin., Rochester, MN; ⁶Cancer Biol., ⁷Quantitative Hlth. Sci., Mayo Clin., Jacksonville, FL; ⁸Radiology, ⁹Lab. Med. and Pathology, ¹⁰Neurol., Mayo Clin., Rochester, MN

Abstract: Aging is the primary risk factor for mild cognitive impairment (MCI) due to Alzheimer's disease and may represent a critical window for slowing or halting progressive

dementia. In brain aging and MCI, limbic white matter is subject to structural and functional changes, but the molecular mediators of these changes remain unclear. Our lab previously discovered that senescent and disease-associated microglia accumulate in aged mouse brain white matter and chemoattract peripheral immune cells, which may exert deleterious inflammatory influence. Novel spatial mapping approaches offer a significant advantage over conventional methods by allowing for the visualization and characterization of senescent cells in their native tissue architecture, revealing their localized influence on white matter microenvironments. Using CosMx spatial molecular imaging, we showed that senescent microglia are particularly enriched in aged mouse hippocampal white matter. As an important translational research focus, we hypothesize that senescent microglia accumulate in the aged *human* hippocampal formation and drive maladaptive inflammatory signaling in white matter, representing an early pathophysiological event in the cascade leading to dementia. To test this, we are analyzing hippocampal formalin-fixed paraffin-embedded sections from MCI and cognitively unimpaired (CU) cases in the Mayo Clinic Study of Aging. We are leveraging the CosMx 6000-plex panel to map spatially defined single-cell gene expression in each section. We then combine cell identity, senescence biomarker expression, cell-cell proximity information, and ligand-receptor inference to precisely define molecular and microenvironment interactions across regions. Following delineation of canonical cell types, our emerging results demonstrate enrichment of senescence markers in microglia and astrocytes. Microglia harboring senescence markers are enriched in white matter. Preliminary ligand-receptor inference demonstrates that white matter microglia express a diverse repertoire of complement, extracellular matrix regulatory factors, and damage associated molecules that may engage receptors on infiltrating immune cells. These findings, consistent with our preclinical data, suggest that senescent glial populations may contribute to immunomodulatory signaling in hippocampal white matter in the context of cognitive decline. We expect our ongoing efforts to reveal molecular mechanisms by which senescent cells contribute to white matter dysfunction underlying cognitive impairment, potentially offering targets for therapeutic intervention.

Disclosures: Y. Ha: None. C.M. Carver: None. J. Shi: None. J.M. Kachergus: None. Y. Liu: None. P. Vemuri: None. E. Thompson: None. A.T. Nguyen: None. M.J. Schafer: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.02/C34

Topic: C.01. Brain Wellness and Aging

Support: UG3 CA275669

Title: Single-cell spatial molecular atlasing defines dominant age-altered populations in mouse brain

Authors: *C. M. CARVER¹, S. L. RODRIGUEZ¹, J. KACHERGUS², J. SHI², E. THOMPSON², M. J. SCHAFER¹;

¹Mayo Clin., Rochester, MN; ²Mayo Clin., Jacksonville, FL

Abstract: The brain endures age-associated structural and functional changes that coincide with greater incidence of white matter degradation and neurological disease. Maladaptive senescent and inflammatory cell fates are potential mediators of age-dependent dysfunction. However, methodological limitations restrict determination of precise cellular and molecular composition changes within distinct age-vulnerable anatomical microenvironments. To address these fundamental knowledge gaps, we applied single-cell CosMx Spatial Molecular Imaging (SMI) to young (4 month) and old (24 month) mouse cortico-limbic samples. CosMx SMI transcript (1000 RNA gene probes) and protein (72 antibody-targeted proteins) assays enabled our analysis of cell populations that emerge and diverge across aging, with preserved spatial context in brain tissue slices. We hypothesized that microglia are a dominant senescent cell type that accumulate in aged white matter. To test this, we developed a panel probing 103 senescence associated genes corresponding to six domains, including cell cycle regulation, nuclear stress, senescence-associated secretory phenotype, senescent cell anti-apoptotic pathways (SCAP), organelle stress, and cell surface markers. The CosMx protein panel included cell-type, neurodegeneration, and custom senescence markers. We derived cell-type identities by unbiased clustering and UMAP algorithms, and cells were registered to anatomical structures. We delineated cell-type subpopulations to determine age-altered and senescent populations and computed proximity interactions based on spatial Euclidean nearest-neighbor networks for each cell. Derived from prevalent cell-cell interactions, we investigated ligand-receptor pairs between cell-type populations. Microglial and mature oligodendrocyte subpopulations in white matter emerged as highly age-altered with high relative senotype scores. White-matter resident astrocytes had high scores for the SCAP domain. Aged barrier cells, including pericytes and ependymocytes exhibited age-dependent gene expression increases that were connected to ligand-receptor relationships with other glial cells. Our emerging results demonstrate profoundly altered cell identities and inferred interactomes with variable senescence characteristics defining core features of spatially-defined subpopulations in the aged mouse brain. Together, we report a single-cell spatial atlas featuring multiple glial classes harboring diverse senescent and age-altered characteristics, with direct inference of modified signaling interactomes, in the aged male and female mouse brain.

Disclosures: C.M. Carver: None. S.L. Rodriguez: None. J. Kachergus: None. J. Shi: None. E. Thompson: None. M.J. Schafer: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.03/C35

Topic: C.01. Brain Wellness and Aging

Support: NIH R01AG057672
NIH RF1AG082223
NIH R01AG072056

Title: Quantitative measures in the hippocampal tail using ex vivo neuroimaging and validated histology

Authors: A. ALEXANDER¹, E. ROSENBLUM¹, N. MERCALDO^{1,3}, E.-M. SMITH¹, A. VAN DER KOUWE^{1,3}, B. FISCHL^{1,3}, M. P. FROSCH^{1,3}, *J. C. AUGUSTINACK^{2,3};

¹Massachusetts Gen. Hosp., Boston, MA; ²Massachusetts Gen. Hosp., Charlestown, MA;

³Harvard Med. Sch., Boston, MA

Abstract: The human hippocampus is known for its role in learning and memory and is divided into three morphological parts: head, body, and tail. In vivo neuroimaging studies have shown that the tail, the most posterior portion of the hippocampus, may be involved in psychiatric disorders. More specifically, volumetric abnormalities in the tail have been reported in patients with depression, bipolar disorder, and panic disorder, yet measures in controls vary substantially. Due to its clinical relevance, the field would benefit from morphometric measures with modern high-resolution imaging to better characterize the hippocampal tail. This study applied high resolution ex vivo MRI validated with histology to illustrate and reconstruct the tail, document volume and length, and add specificity to existing nomenclature. We obtained and analyzed 10 human brain hemispheres: 5 left (3 female, 2 male) and 5 right (2 female, 3 male). Hemispheres were scanned in a whole-body ultra-high-field 7.0 T Siemens Magnetom at 120³ μm³ and manually labeled for tail. The manual labeling of the MRI was guided by histology sections. The tissue was blocked and sectioned coronally at 50 μm thickness and stained for Nissl substance with thionin. We classified six coronal anterior-posterior levels within the hippocampal tail consisting of: (1) anterior tail, (2) fasciolar initium, (3) fasciolar junction, (4) posterior tail, (5) separated tail, and (6) tail terminus. The shape and volume of the tail was characterized with 3D reconstructions based on 120³ μm³ resolution ex vivo MRI. The mean tail volume of our sample set was 661.2 mm³ ± 150.7 mm³ (n=10). We compared tail volume, length, and shape with hemisphere, sex, and age. The hippocampal tail volume in the left versus right hemispheres was not significantly different (Mann-Whitney test, p= 0.8413). The samples from male brains showed a mean tail volume of 667.0 mm³ while tail samples from female brains averaged 655.4 mm³. Tail volume was not significantly different between sexes (Mann-Whitney test, p= >0.999) and did not correlate with age (Spearman's rho, r = 0.3161, p = 0.3711). We also analyzed the number of digitations in the hippocampal head (pes) and tail (Gyrus of Andreas Retzius (GAR)). The number of pes (hippocampal head) did not vary much, but the number of GAR (hippocampal tail) varied substantially among individuals. These validated findings characterize the hippocampal tail in cognitive controls and identify variability in the human brain that will benefit and inform clinical research pertaining to mental health.

Disclosures: A. Alexander: None. E. Rosenblum: None. N. Mercaldo: None. E. Smith: None. A. Van Der Kouwe: None. B. Fischl: None. M.P. Frosch: None. J.C. Augustinack: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.04/C36

Topic: C.01. Brain Wellness and Aging

Support: R01AG072056
RF1AG082223
R01AG057672

Title: Filling in the gaps: neuronal counts in hippocampal CA1 in female cognitive controls

Authors: *E.-M. C. SMITH¹, A. M. ALEXANDER¹, E. W. ROSENBLUM¹, N. MERCALDO^{1,3}, M. P. FROSCH^{2,3}, J. C. AUGUSTINACK^{1,3};

¹Radiology, ²Neuropathology, Massachusetts Gen. Hosp., Boston, MA; ³Harvard Med. Sch., Boston, MA

Abstract: Hippocampal subfield CA1, also known as Sommer's sector, is known to be vulnerable to hypoxia and neuronal death. CA1 is also susceptible in Alzheimer's disease (AD); it receives input from the entorhinal cortex, which is affected by phosphorylated tau deposits in early AD progression. Due to these vulnerabilities and other factors, counting CA1 in control samples is needed. Previous studies have quantified total neuron counts in CA1, but these studies primarily focused on male samples only and did not consider laterality. This study aims to establish baseline neuron counts in CA1 for both sexes in samples with little to no tau pathology. We performed stereology on Nissl stained sections using the optical fractionator (n = 10, 5 females, 5 males, median age = 64.5 ± 11.75 years (IQR)) on postmortem human brain hemispheres. All samples were cognitive controls at the time of death (Braak and Braak stages 0-II). Samples were sectioned coronally at 50 μm and every 30th slice was counted throughout the hippocampal head and body. The counting frame was 50 x 50 μm and the sampling grid was 900 x 900 μm . Coefficient of error under 0.10 was achieved for all samples, which is the ideal standard for stereology. *Ex vivo* MRI were collected at 1 mm isotropic resolution using a Siemens 3 T Trio MRI. *Ex vivo* MRI was manually labeled and used to calculate hippocampal volume of the head and body on a subset of n = 7 samples. The mean total neuron count in CA1 was 5.64 ± 0.56 million neurons (S.E.M.) (n = 10). Assessing sex as a biological variable, the mean total neuron counts for males was 5.37 ± 0.36 million neurons (n = 5) and 5.91 ± 0.11 million neurons (n = 5) for females. The mean total neuron counts for left and right hemispheres were 5.45 ± 0.94 (n = 6) and 5.93 ± 0.23 million neurons (n = 4), respectively. The total neuron counts in females and left hemispheres showed greater variability. No significant differences were found between sex, hemisphere, sex/hemisphere, age, or Braak stage (tau) for total neuron count in CA1. CA1 total neuron count positively correlated with volume (*ex vivo* MRI, 1 mm, manual labeling) in hippocampal head and body (Pearson correlation, $r = 0.8300$, $p = 0.0208$). These results agree with past studies and add vital assessments of both sexes and respective hemispheres as biological variables. Accurate baseline counts for additional demographic groups, particularly females given their increased vulnerability to AD, was needed. These results establish neuron counts in CA1 in both sexes and respective hemispheres in cognitive controls with the optical fractionator stereology method.

Disclosures: E.C. Smith: None. A.M. Alexander: None. E.W. Rosenblum: None. N. Mercaldo: None. M.P. Frosch: None. J.C. Augustinack: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.05/C37

Topic: C.01. Brain Wellness and Aging

Support: R01AG072056
RF1AG082223
R01AG057672

Title: Total neuron counts versus subfield volume: a stereological study in entorhinal cortex controls

Authors: *E. ROSENBLUM¹, M. P. FROSCH^{2,3}, J. C. AUGUSTINACK^{1,3};
¹Radiology, ²Pathology, Massachusetts Gen. Hosp., Boston, MA; ³Harvard Med. Sch., Boston, MA

Abstract: Tau pathology in Alzheimer's disease (AD) impacts entorhinal cortex (EC) early; however, pathology does not affect the EC homogeneously in disease progression. The lateral posterior regions exhibit tau burden first (subfield ECs), while anterior subfields ER and EI fail later in disease progression. The resilience in certain subfields may delay AD and suggest an opportunity for further development. We assessed and compared the result of total neuron counts in the whole EC to those in three subfields, ER, EI, ECs with respect to overall territory (volume) (Oltmer et al., 2022). We counted neurons in entorhinal layer II in n = 5 postmortem human samples. Samples were cognitive controls (BB0) and died from non-neurological causes. Sample ages ranged from 52 - 68 years old, mean age = 59.4 ± 9.20 years, n = 1 female, n = 4 males. Medial temporal lobe blocks were cryoprotected and sectioned at 50 μm on a freezing sliding microtome. Samples were immunostained for phosphorylated tau (CP13) and staged according to Braak and Braak severity. Tissue sections were also Nissl stained and parcellated for EC subfields based on the protocol detailed in Insausti et al., 1995. Total neuron counts were obtained using the Optical Fractionator method with the following parameters: every 30th section was stained for Nissl and counted; the disector height was 10 μm and a sampling grid (450 x 450 μm) was overlaid to determine the location of the counting frames (75 x 75 μm). Mean tissue thickness was 18.9 μm , which accommodated the 3 μm guard zones (top and bottom). The mean neuron count ($\pm$ SD) in EC layer II was $1,093,774 \pm 194,530$ and the range was 873,263 - 1,306,842. The mean total neuron count in ER, EI and ECs was $155,838 \pm 22,080$, $160,446 \pm 18,312$ and $109,086 \pm 194,530$, respectively. When compared to the entire EC, ER neuron counts were 14.25%, EI was 14.67% and ECs was 9.97% of the total EC neuron counts. The subfields ER and ECs neuron count percentages were similar to the volume (territory) percentage of these subfields (14.06 % and 10.99%, respectively), but the EI neuron count percentage was much

lower than the mean volume percentage (23.36%) versus 14.67% of total neurons. Together, these subfields account for ~40% of neurons in whole EC and may be good predictors of overall number of neurons in EC. Since EI has a larger volume than ER, but similar neuron counts to ER, this suggests the white matter makes up a larger portion of the volume in EI. Resilience in ER and EI, compared to ECs, may come from higher initial neuron counts. These findings may suggest a relationship to the white matter in entorhinal cortex and possible resilience.

Disclosures: E. Rosenblum: None. M.P. Frosch: None. J.C. Augustinack: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.06/C38

Topic: G.03. Stress and the Brain

Support: NIH T32 NS045540

Title: Tracing the origins of CRH expressing projections to the paraventricular nucleus of the thalamus

Authors: *J. M. MENDOZA¹, A. FLORIOU-SERVOU², Y. CHEN³, T. Z. BARAM⁴;
¹Anat. and Neurobio., Univ. of California, Irvine, Irvine, CA; ²Dept. of Anat. & Neurobio., UC Irvine, Irvine, CA; ³Pediatrics, Dept. of Pediatrics, Univ. of California-Irvine, Irvine, CA;
⁴Anatomy/Neurobiology; Pediatrics, Univ. of California Irvine, Irvine, CA

Abstract: Rationale: The Paraventricular nucleus of the thalamus (PVT) is the only region in which more cells are activated by early-life adversity (ELA) compared to other early-life experiences. The PVT is a crucial component of the emotional processing network and adjudicates stress and reward behaviors in the context of remote prior stress. A larger proportion (50%) of PVT cells activated during ELA express corticotropin-releasing hormone receptor 1 (CRHR1) compared to cells activated during typical rearing (~20%). Importantly, the ligand for CRHR1, CRH is released by stress in several brain regions including amygdala and hippocampus. Therefore, it is plausible that CRH release in PVT might govern the activation of CRHR1 cells however, the source of PVT-CRH is unknown. **Methods:** To trace the CRH inputs to the PVT we administered a retrograde CRE-dependent virus into the anterior or posterior PVT of CRH-IRES-CRE mice or CRH-IRES-CRE x TdTomato offspring. After 6 weeks, the mice were perfused and the brain was sectioned and imaged in 70 µm intervals, to search for retrogradely labeled neurons. We then administered an anterograde, CRE-dependent virus to validate that retrogradely labeled neurons send axonal projections to the PVT. The anterograde experiment is repeated again with the inclusion of administering a non-selective retrograde AAV into the PVT to further validate the afferent CRH+ projection. **Results:** 1) Retrogradely labeled neurons were found in the amygdala, the parabrachial nucleus (PBN) and the pontine central grey area and especially in the Barrington nucleus. 2) Anterograde tracing from the PBN,

revealed dense axon fibers in the PVT, validating this CRH projection. 3) results from the amygdala as well as proximal thalamic nuclei are pending. **Conclusions:** Anterograde and retrograde viral tracing show that the PVT receives CRH inputs from the brain stem, particularly the PBN. Another area that could potentially send CRH projections to the PVT is the Barrington nucleus (BN) that is also targeted during anterograde tracing due to its proximity to the PBN and is strongly labeled by the virus. Both the PBN and the BN receive inputs from the spinal cord, and could relay stress-related stimuli from the environment to the PVT. Funding: T32 NS045540

Disclosures: J.M. Mendoza: None. A. Floriou-Servou: None. Y. Chen: None. T.Z. Baram: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.07/C39

Topic: C.01. Brain Wellness and Aging

Support: R01AG072056
RF1AG082223
R01AG057672

Title: Neuronal vulnerability in aging and Alzheimer's disease

Authors: *J. CHASE¹, J. ROY¹, E. ROSENBLUM¹, M. P. FROSCH^{2,3}, J. C. AUGUSTINACK^{1,3};

¹Massachusetts Gen. Hosp., Charlestown, MA; ²Neuropathology, Massachusetts Gen Hosp, Boston, MA; ³Harvard Med. Sch., Boston, MA

Abstract: Entorhinal cortex (EC) is an early site for tau pathology in Alzheimer's disease (AD). Tau pathology targets layer II, which is the site of conversion from healthy aging to AD. It has been demonstrated that pyramidal neurons in isocortex were particularly vulnerable to phosphorylated tau (p-tau). EC layer II is a mixture of pyramidal and stellate neurons, however, the vulnerability of neuron subtypes has not been fully established in EC. Moreover, EC subfields vary such that some show early vulnerability to tau pathology (ECs) while others show prodromal resilience (ER, EMI, and EI). This study aims to determine the baseline of pyramidal neurons in tau negative controls, and to understand neuronal vulnerability to p-tau. Ten cognitive control postmortem brain hemispheres (4 left, 6 right) were blocked for EC. Samples included 5 females and 5 males aged 52 - 84 (63.9 ± 10.58 ; mean $\pm$ SD) years, immunostained for p-tau (CP13, 1:200 dilution) and staged according to Braak and Braak (BB) severity. Four of Insausti's EC subfields, rostral (ER), medial intermediate (EMI), intermediate (EI), and caudal (ECs), were analyzed. Charting data was collected on three tissue sections per subfield and three islands per section (i.e. nine islands per subfield and 36 islands per sample). We assessed cellular staining (Nissl) to visualize all neurons throughout EC. We further developed a protocol to differentiate

between neuron types based on morphology: 1) We define a pyramidal neuron to have a strong apical dendrite, two to three other dendrites directly opposing the apical, and a triangular soma shape, 2) we define a stellate neuron as lacking a dominate apical dendrite and instead having five or more dendrites throughout a star or rectangular shaped soma. This study finds that, at baseline, islands consist of an average of 62% (± 0.09) (SD) pyramidal neurons ($n = 6$ cases) with an average of 51 ± 27 (SD) neurons charted per island; BB I cases ($n = 2$), average pyramidal percentage was 62% (± 0.09), and BB II cases ($n = 2$) were 58% (± 0.08) pyramidal. Subfields ER and ECs showed significant differences between BB0 (ER 64% ± 8.3 ; ECs 62% ± 10.1) and BB IIs (ER 54% ± 5.7 ; ECs 58% ± 6.8) (Kruskal-Wallis Test, ER $p = 0.004$; ECs $p = 0.04$). Pyramidal neurons in ER and ECs may be particularly vulnerable to AD pathology. This study shows evidence that pyramidal neurons represent the primary neuron type of entorhinal layer II islands among tau negative, cognitive control samples. These results highlight vulnerabilities on the cellular level at the earliest stages of disease pathology.

Disclosures: J. Chase: None. J. Roy: None. E. Rosenblum: None. M.P. Frosch: None. J.C. Augustinack: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.08/C40

Topic: C.01. Brain Wellness and Aging

Support: Consejo Nacional de Ciencia y Tecnología (CONACYT) FOSEC SEP-INVESTIGACIÓN BÁSICA A1-S-26479
The International Society for Neurochemistry-CATEGORY 1C: Return Home
SECIHTI 800824
SECIHTI 1079765
SECIHTI 1241800
SECIHTI 1241696
SECIHTI 626561

Title: Nuclear and cytoplasmic Mouse ID associated 1 (MIDA1) protein varies in neurons and astrocytes across the different hippocampal regions and exhibits age-related changes

Authors: *V. M. RUIZ-RODRÍGUEZ¹, A. O. CUELLAR SANTOYO², O. A. PATRÓN SOBERANO⁶, K. HERNANDEZ-BALDERAS³, C. GALINDO⁴, B. VARGAS³, S. A. NIÑO, Sr.⁷, A. M. ESTRADA SANCHEZ⁵;

¹Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico; ²Biología Mol., IPICYT, San Luis Potosi, Mexico; ³División Biología Mol., ⁴División de Biología Mol., IPICYT, San Luis Potosí, Mexico; ⁵División de Biología Mol., IPICYT, San Luis Potosi, Mexico; ⁶Mol. Biol., Inst. Potosino de Investigación Científica y Tecnológica A.C., San Luis

Potosí, Mexico; ⁷Lab. of Cell. and Neuronal Dynamics, CENTER FOR GEROSCIENCE, BRAIN HEALTH AND METABOLISM, San Luis Potosi, Mexico

Abstract: Nuclear Mouse ID Associated 1 (MIDA1), also known as Hsp40/DNAJC2 and ZRF1, plays a key role in establishing neural progenitors in the brain. In the cytoplasm, MIDA1 ensures proper protein folding, which, if disrupted, can lead to protein misfolding and ultimately neurodegeneration. Thus, MIDA1 is crucial for maintaining brain cell homeostasis. However, it remains unclear whether neurons and astrocytes express MIDA1 equally, whether the distribution of MIDA1 between the nucleus and cytoplasm differs, and if this difference changes with age. Therefore, we evaluated MIDA1 content and distribution in neurons and astrocytes of the CA1, CA3, and dentate gyrus (DG) in 3- and 12-month-old mice. The results indicated that cytoplasmic MIDA1 content is greater in neurons and astrocytes at both ages, with higher levels observed in the older mice. An overall reduction of MIDA1 in the nucleus of neurons was noted, while only the CA1 and CA3 areas displayed increased cytoplasmic MIDA1. In contrast, astrocytes exhibited similar levels of MIDA1 in the nucleus across the hippocampal regions analyzed. However, astrocytes from the CA1 and CA3 regions in the 12-month-old group showed increased cytoplasmic MIDA1 content. Lastly, a comparison of MIDA1 content between neurons and astrocytes revealed that astrocytes have lower MIDA1 levels in the nucleus at both ages. Notably, at 12 months, cytoplasmic MIDA1 levels were higher in astrocytes than in neurons. Given that the function of MIDA1 depends on its subcellular location, our results suggest that more dynamic changes in MIDA1 content occur in the cytoplasm across different hippocampal areas, becoming more pronounced in astrocytes at 12 months. Therefore, MIDA1's role as a chaperone might be crucial as astrocytes and neurons age, which coincides with age-related cognitive deficits as evaluated by the novel object recognition test.

Disclosures: V.M. Ruiz-Rodríguez: None. A.O. Cuellar Santoyo: None. O.A. Patrón Soberano: None. K. Hernandez-Balderas: None. C. Galindo: None. B. Vargas: None. S.A. Niño: None. A.M. Estrada Sanchez: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.09/C41

Topic: C.01. Brain Wellness and Aging

Support: P51 OD-011092
RF1 AG-062220
RF1 AG-06283
RF1 AG-043640

Title: Partial coincidence of amyloid plaques and Aquaporin-1 positive astrocytes with advanced age in rhesus macaques

Authors: *O. E. STAYER-WILBURN¹, D. L. ROSENE², P. L. SHULTZ³, A. VITANTONIO⁴, C. DIMOVASIL⁵, J. MATTISON⁶, K. VAUGHAN⁷, H. F. URBANSKI⁸, S. G. KOHAMA⁹;

¹OHSU / ONPRC, Beaverton, OR; ²Anat. & Neurobio., Boston Univ. Grad. Program In Anat. & Neurobio., Boston, MA; ³Anat. and Neurobio., Sch. of Med., Boston, MA; ⁴Pharmacology, Physiology, and Biophysics, Boston Univ., Boston, MA; ⁵Anat. & Neurobio., Boston Univ. Sch. of Med., Boston, MA; ⁶Natl. Inst. on Aging, Dickerson, MD; ⁷Natl. Inst. on Aging, Bethesda, MD; ⁸Div. Neurosci., Oregon Natl. Primate Res. Ctr., Beaverton, OR; ⁹ONPRC, Beaverton, OR

Abstract: Aging causes physiological and anatomical changes in the primate brain, including astrogliosis, accumulation of amyloid-beta and phosphorylated tau proteins with a greater risk of developing neurodegenerative disease. Previously we reported the upregulation of the water channel Aquaporin-1 (AQP1) in the prefrontal cortex (PFC) of the oldest-old (>25 years) rhesus macaques from the NIA Caloric Restriction study. Because AQP1 is normally found in brain white matter, glia limitans, and choroid plexus, but increases in the cortex with glioma, stroke, traumatic brain injury, and neurodegenerative lesions, the increase of cortical AQP1 with advanced age in the primate brain may involve similar pathophysiological processes. Moreover, because of prior reports of astrocytic GFAP increases in the macaque PFC by middle-age, the subsequent limited astrocytic expression of AQP1 indicates a selective, progressive process. Qualitatively, AQP1+ astrocytes also overlapped temporally with the appearance of amyloid, as seen in clinical studies, suggesting a possible interaction. The current study employed multiplex immunofluorescence to better understand the timing, distribution and overlap of astrogliosis, amyloidosis, and AQP1 expression. Immunofluorescence co-labeling of AQP1, beta-Amyloid (A β), GFAP, as well as DAPI nuclear stain was performed on PFC coronal sections from male and female rhesus macaques from the NIA CR Study (22 to 42 years old, n=30). Cortical GFAP levels were already elevated in the youngest animals, with AQP1 levels peaking in the third decade of life. Enriched AQP1 structures included descending pial blood vessels, the white-gray matter interface, and clusters of reactive astrocytes. As noted before, AQP1 colocalized with GFAP, confirming expression in astrocytes. Although amyloid plaque load and colocalization with AQP1 varied across individuals and subregions, about 50% of amyloid plaques colocalized with AQP1 across all PFC subregions. The anterior cingulate cortex and gyrus rectus were the most enriched regions across all animals. Many plaques were also associated with GFAP+ astrocytes in the absence of AQP1, and fewer were observed without GFAP or AQP1. These results confirm that AQP1 is expressed late in the lifespan in a subset of reactive astrocytes, in the absence and presence of amyloid plaques, suggesting differential expression with age and region are dependent upon other factors that dictate colocalization.

Disclosures: O.E. Stayer-Wilburn: None. D.L. Rosene: None. P.L. Shultz: None. A. Vitantonio: None. C. Dimovasili: None. J. Mattison: None. K. Vaughan: None. H.F. Urbanski: None. S.G. Kohama: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.10/C42

Topic: C.01. Brain Wellness and Aging

Support: AFSP BlueSky Grant BSG-0-181-23
TRDRP Grant T32IR5211

Title: Cell-specific telomere length in post-mortem human brain of subjects with major depressive disorder

Authors: F. MAMDANI¹, R. KUBA², B. NGUYEN¹, *A. SEQUEIRA³;
¹Psychiatry and Human Behavior, ²Univ. of California, Irvine, Irvine, CA; ³Psychiatry and Human Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Major depressive disorder (MDD) is a highly prevalent disorder affecting approximately 11% of the general population, with rates ranging between 3.2 -4.6% within a given year. Several studies have shown that stressful life events and chronic stress are risk factors for MDD. It is also known that stress can lead to accelerated cellular ageing resulting in shortening of telomeres. In recent studies stress and depression have been associated with reductions in hippocampal volume and decreased neurogenesis in humans and animal models. Telomeres are special repetitive sequences of DNA located at the end of chromosomes which preserve DNA integrity, but they naturally shrink with age/cell divisions, and their loss eventually leads to chromosomal instability and cell death. We first reported a significant reduction in telomere length (TL) in the hippocampus of MDDs compared to controls a few years ago. This finding remained significant following correction for age, pH, and post-mortem interval (PMI). These results suggest a stress-mediated acceleration of cellular ageing within the hippocampus of MDDs. However, since bulk tissue homogenates were used, the cellular specificity of these MDD-Specific changes were not elucidated. This is of interest since the hippocampus and its sub-regions are composed of non-dividing neurons and dividing cells, such as glia, and both these classes of cells can undergo telomere shortening. To answer this question, we measured cell-specific telomere length in the hippocampus of 10 MDD-Suicide subjects (5 males and 5 females), 10 MDD-Non-Suicide subjects (5 males and 5 females), and 10 controls (5 males and 5 females) using Fluorescence Assisted Nuclei Sorting to isolate four cell types (N=120 samples): neurons, microglia, oligodendrocytes, and astrocytes. DNA was extracted for each cell population and TL is measured by a qPCR-based assay. In addition to diagnosis effects (MDDs versus controls) on TL, the impact of suicide status (MDD-Suicide versus MDD-Non-Suicide) and gender (females versus males) on TL is analyzed. This project provides insight into cell-specific mechanisms of telomere attrition in the hippocampus of MDD patients and novel evidence for an interaction between suicide and accelerated cellular aging.

Disclosures: F. Mamdani: None. R. Kuba: None. B. Nguyen: None. A. Sequeira: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.11/Web Only

Topic: C.01. Brain Wellness and Aging

Support: Cure Alzheimer's Fund

Title: Single-cell, direct in situ visualization of the 3d genome of cell senescence using paintscape™

Authors: *X. SUN^{1,2}, U. S. TULU³, H. NGUYEN³, S. CHATTORAJ³, J. DUNNE³, T. RUSSO⁴, M. RIESSLAND⁴, M. ORR^{1,2,5,6};

¹Neurol., Washington Univ. in St. Louis, Saint Louis, MO; ²Bruker Spatial Biol. Ctr. of Excellence, Saint Louis, MO; ³Bruker Spatial Genomics, Inc., San Jose, CA; ⁴Dept. of Neurobio. and Behavior, Ctr. for Nervous Syst. Disorders, Stony Brook Univ., Stony Brook, NY; ⁵St Louis VA Med. Ctr., Saint Louis, MO; ⁶Tracy Family SILQ Ctr., Saint Louis, MO

Abstract: Cellular senescence is a complicated stress response characterized by cell cycle arrest, resistance to apoptosis, and secretion of various proinflammatory molecules collectively known as the senescence-associated secretory phenotype (SASP). In the aging brain, many cell types become senescent, particularly under disease and neurodegenerative conditions. Senescence is highly heterogeneous, with features that vary depending on the initiating stress, cell identity, and progression stage. Senescent cells undergo extensive nuclear remodeling, including nuclear enlargement, alterations to the nuclear lamina, and global chromosomal reorganization. Recent advances in 3D genome mapping technologies have revealed many chromosomal alterations in senescent cells, such as compartment switching, changes in lamina-associated domains, and the formation of senescence-associated heterochromatin domains. However, a comprehensive, high-resolution view of 3D genome reorganization at the single-cell level has been lacking. In this project, we applied a novel jebFISH™ protocol on the PaintScape™ platform to directly visualize such changes in different senescent cells *in situ* at single-cell, sub-population, and population levels. We generated chromosome-specific spatial traces in brain cell lines following BrdU-induced senescence *in vitro*, revealing specific 3D structural changes and inter-chromosomal interaction patterns. We validated the senescent state through multiple assays, including SA-β-gal staining, immunostaining for canonical senescence markers, and profiling of SASP factors in conditioned media. We compared the chromosomal architecture between proliferating and senescent cells, to uncover shared and cell-type-specific patterns of chromosomal reorganization during senescence. In summary, this approach provides direct visualization and quantitative assessment of genome topology changes during senescence. Our findings underscore the utility of PaintScape for dissecting 3D genome reorganization in diverse senescent brain cell populations and offer a structural framework for understanding regulatory heterogeneity in brain aging and neurodegeneration.

Disclosures: X. Sun: None. U.S. Tulu: A. Employment/Salary (full or part-time): Bruker. H. Nguyen: A. Employment/Salary (full or part-time): Bruker. S. chattoraj: A. Employment/Salary (full or part-time): Bruker. J. Dunne: A. Employment/Salary (full or part-time): Bruker. T. Russo: None. M. Riessland: None. M. Orr: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.12/C43

Topic: C.01. Brain Wellness and Aging

Support: P51 OD011092
K01 OD31899
K01 OD31899-03S1

Title: Integrative long- and short-read sequencing reveals age-associated isoform expression changes in the rhesus macaque hippocampus

Authors: *V. HARPER-ALEXANDER¹, S. PETERSON², S. G. KOHAMA², D. RAM¹;
¹Univ. of Central Florida, Orlando, FL; ²Oregon Natl. Primate Res. Ctr., Beaverton, OR

Abstract: Alternative splicing plays a critical role in transcriptome complexity, and age-related changes in isoform expression may contribute to brain aging and neurodegeneration. However, isoform-level resolution is often limited by short-read RNA sequencing alone. This proof-of-concept study aimed to characterize age-related isoform expression changes in the hippocampus of rhesus macaques by integrating long-read and short-read RNA sequencing approaches. Hippocampal RNA was collected from young (n=3; mean age=5 years old) and aged (n=3; mean age=25 years old) male rhesus macaques. Oxford Nanopore Technologies long-read RNA sequencing captured full-length transcripts with read qualities exceeding Q20, while Illumina short-read sequencing provided high-depth quantification. Isoform-level expression was quantified, and differential expression analysis was conducted to identify age-associated changes in gene and isoform expression. Long-read sequencing enabled the identification of numerous differentially expressed isoforms, particularly in genes related to immune regulation. Several genes demonstrated changes in isoform expression with age, including those involved in neuroinflammatory signaling, RNA processing, and membrane trafficking. Notably, major histocompatibility complex, class I, A3 (*MAMU-A3*) was significantly differentially expressed at both the gene and isoform levels, highlighting immune pathway involvement in aging. Conversely, Regulator of G-protein Signaling 10 (RGS10), a gene associated with age-dependent dysregulation of neuroimmune interactions, showed significant isoform-level changes without corresponding gene-level differences. Specifically, the data showed an upregulation of the non-canonical RGS10 transcript XM_015148166.2, which encodes an N-terminally extended protein that may impact its functional properties. Notably, these significant age-related isoform changes would have been missed by short-read data alone, underscoring the value of long-read sequencing for accurate transcript identification. Our findings highlight age-associated isoform expression changes in the primate hippocampus and demonstrate the complementary strengths of long-read and short-read sequencing in capturing isoform dynamics. These results provide a foundation for understanding aging in the primate brain at isoform-level resolution.

Disclosures: V. Harper-Alexander: None. S. Peterson: None. S.G. Kohama: None. D. Ram: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.13/C44

Topic: C.01. Brain Wellness and Aging

Support: Beckman-Brown Interdisciplinary Fellowship
NIH NIA R01AG078797
NIH NIDA P30DA018310
NIH S10OD032242

Title: Age Related Changes in Spatial Distribution of Isomeric Glycolipid Metabolism in Rat Brain

Authors: *H.-C. CHAO^{1,2}, M. ASADIAN^{1,2}, S. S. RUBAKHIN^{1,2}, F. LAM^{1,3}, J. V. SWEEDLER^{1,2};

¹Beckman Inst. for Advanced Sci. and Technol., Urbana, IL; ²Dept. of Chem., ³Dept. of Bioengineering, Univ. of Illinois-Urbana Champaign, Urbana, IL

Abstract: Cerebrosides (CBs) are essential glycolipids involved in neurodevelopment, cell signaling, and age-associated metabolic processes in the brain. These lipids consist of a ceramide backbone linked to glucose or galactose, forming either glucosylceramides (GlcCer) or galactosylceramides (GalCer), respectively. Although structurally similar, these isomeric species have distinct biological roles. Conventional mass spectrometry methods cannot resolve these isomers, limiting insights linking their spatial distributions and function in neurobiology. To address this challenge, we developed a MALDI-TIMS imaging platform combining on-tissue phospholipase C (PLC) digestion, MALDI-2 post-ionization, and ion mobility-enhanced ion optics. This approach enables direct, in situ separation and spatial mapping of CB isomers in brain tissue without chromatography. PLC selectively removes phospholipids, reducing ion suppression, while MALDI-2 enhances glycolipid ionization, enabling robust detection and imaging of low-abundance CB species. Using rat brains from three age groups (61, 180, and 364 days; n = 4 per group), we profiled 36 m/z features corresponding to 45 CBs, including five distinct isomeric groups. Imaging revealed GalCers localized predominantly in the corpus callosum and cerebellum, whereas GlcCers displayed broader, complementary patterns. These spatial distinctions, visualized for the first time at the isomer level, are inaccessible by standard imaging techniques. Age-dependent changes in isomer-specific CBs were also observed. GalCer 36:1 significantly varied with age (ANOVA, $p < 0.05$), while pooled HexCer 36:1 (without isomer resolution) showed no difference, highlighting the value of isomer-resolved analysis. Further, age-related alterations extended to CB-derived metabolites. Sulfatides 36:1 (from GalCer), showed the most pronounced decline with age ($p < 0.05$). GM3 gangliosides (from GlcCer) also declined with age. These metabolites mirrored the spatial distributions of their CB precursors. Ceramides, precursors to both isomeric CBs, showed mild increases in the overall brain, with elevated levels in the hypothalamus. Moreover, GalCer co-localized with oligodendrocyte-rich regions, confirmed using mass-tag labeling of myelin-associated proteins, suggesting that declining GalCer levels may reflect demyelination, a hallmark of brain aging.

This study demonstrates the unique advantage of isomer-resolved MSI in uncovering spatially distinct metabolic changes and offers a valuable tool for studying neurodegeneration and aging.

Disclosures: H. Chao: None. M. Asadian: None. S.S. Rubakhin: None. F. Lam: None. J.V. Sweedler: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.14/C45

Topic: C.01. Brain Wellness and Aging

Support: NIH grant U54 AG054345
Diana Davis Spencer Foundation

Title: Proteomic aging trajectories across mouse strains mirror human brain aging heterogeneity

Authors: *A. UYAR¹, C. PAISIE¹, M. KOSTICH¹, M. MACLEAN², G. R. HOWELL², G. W. CARTER²;

¹The Jackson Lab. for Genomic Med., Farmington, CT; ²The Jackson Lab., Bar Harbor, ME

Abstract: Aging is the primary risk factor for neurodegenerative diseases, yet the molecular underpinnings of heterogeneous brain aging trajectories remain incompletely understood. Here, we employed TMT-based quantitative proteomics and N- and O-linked glycoproteomics to profile brain aging across nine genetically diverse mouse strains at 4, 12, and 24 months of age, representing young, middle-aged, and old time points. Using linear modeling and gene set enrichment analysis (GSEA), we identified both conserved and strain-specific proteomic signatures of aging and linked them to variability observed in human brain aging and Alzheimer's disease (AD) susceptibility. Proteome-wide analysis revealed striking strain-specific differences: some strains (e.g., CAST, WSB) showed upregulation of immune and metabolic pathways, while others (e.g., B6, NOD) exhibited downregulation of synaptic and mitochondrial proteins. Despite this diversity, we identified a shared set of upregulated proteins across strains, including *VCAN*, *PSAP*, *SPP1* and *PTGDS*, involved in extracellular matrix remodeling, lysosomal function, and neuroinflammation. These proteins are also altered in human aging and AD, underscoring their relevance to conserved brain aging mechanisms. A complementary set of downregulated proteins, such as *TIMM22*, *MRPL40* and *COX6B1*, reflected mitochondrial decline with age. GO enrichment further distinguished core biological processes (e.g., oxidative stress response, glial activation) from strain-specific pathways such as mitochondrial transport and synaptic signaling. In parallel, we performed N- and O-linked glycoproteomic profiling on the same samples to investigate post-translational modifications. Age-dependent changes in glycosylation of key proteins, particularly those involved in immune signaling and synaptic function, varied markedly across strains, suggesting that genetic background also influences post-translational regulation during brain aging. Given increasing evidence from human studies

that altered glycosylation contributes to aging and AD pathology, our results suggest that post-translational modifications may explain an additional layer of molecular heterogeneity in brain aging, beyond gene expression or protein abundance alone. Altogether, these findings support the concept that genetic background shapes molecular aging trajectories, echoing the variability seen in human cognitive aging and AD risk, and highlight the value of integrative multi-omics approaches in uncovering molecular mechanisms underlying resilience and vulnerability to age-related neurodegeneration.

Disclosures: A. Uyar: None. C. Paisie: None. M. MacLean: None. G.R. Howell: None. G.W. Carter: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.15/C46

Topic: C.01. Brain Wellness and Aging

Support: Z01-AG000511

Title: Multi-omic profile of senescence in human brain cell types

Authors: *K. ONWUZURIKE¹, M. SALAMINI¹, C. ANERILLAS², M. GOROSPE¹;
¹Lab. of Genet. & Genomics, Natl. Inst. of Hlth. - Natl. Inst. on Aging, Baltimore, MD; ²Ctr. de Biología Mol. Severo Ochoa, Madrid, Spain

Abstract: Neurodegenerative diseases remain major clinical challenges, and understanding their molecular underpinnings is critical for developing new therapies. Recent studies have identified senescent brain cells in patient and animal models of neurodegeneration, suggesting that senescent cells may contribute to disease progression. However, the mechanisms by which these cells become senescent and influence pathology are poorly understood.

Senescence is defined by cell cycle arrest in response to stress, but senotypes vary depending on the cell type and senescence-inducing trigger. Thus, comprehensive molecular characterization of senescent brain cells is necessary. A recently developed senescence catalogue profiled 14 human cell types across multiple stressors, providing a foundation for understanding shared and cell-specific pathways.

To build on this work, we aim to expand the catalogue to include brain cell types implicated in neurodegeneration such as astrocytes, microglia, oligodendrocytes, and brain endothelial cells. So far, we generated transcriptomic and proteomic profiles for ionizing radiation-induced senescence (IRIS) and etoposide-induced senescence (ETIS) in human cultured astrocytes. We also optimized senescence conditions following exposure of human astrocytes to doxorubicin, H₂O₂, CoCl₂, and HRASV12, and we validated senescence-associated transcriptomic profiles by reverse transcription (RT)-qPCR analysis. Preliminary results demonstrate the presence of shared senescence multiomic signatures in ETIS and IRIS conditions.

Ongoing work will further characterize the remaining brain cell types through phenotypic assays and obtain transcriptomic and proteomic datasets for all the mentioned senescence triggers. We will also expand our list to include pathologically relevant senescent triggers such as amyloid β and tau oligomers. By extending the senescence atlas of brain cell types, we aim to better understand how senescent cells contribute to neurodegenerative disease and to guide the development of targeted therapeutic strategies.

Disclosures: K. Onwuzurike: None. M. Salamini: None. C. Anerillas: None. M. Gorospe: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.16/C47

Topic: C.01. Brain Wellness and Aging

Title: Spatial Multiomic Profiling of Trans-Differentiated and iPSC-Derived Neurons Reveals Differential Aging Markers and Divergent Morphology

Authors: *D. PANT¹, T. WOLF², S. LYMER²;

¹Biol. Sci., Univ. of California San Diego, La Jolla, CA; ²Element Biosci., San Diego, CA

Abstract: Understanding the molecular mechanisms of aging is essential for uncovering the basis of age-related diseases and advancing regenerative medicine. Cellular reprogramming models are powerful tools for studying human aging, each with distinct advantages and limitations. Induced pluripotent stem cell (iPSC)-derived neurons are reprogrammed prior to differentiation and may lose key hallmarks of aging. In contrast, trans-differentiated neurons bypass the pluripotent stage, potentially preserving age-related features. To investigate these differences, we used the Element Biosciences AVITI24™ platform, applying Teton™ CytoProfiling technology with the Human Neuroscience Panel for single-cell and spatial co-detection of RNA, protein, phospho-protein and cell morphology at subcellular resolution. The panel includes markers relevant to neurodegenerative, neuropsychiatric, and neuro-oncology research. We analyzed two 12-well-format flow cells: one containing trans-differentiated neurons and the other iPSC-derived neurons. Morphological features were visualized using a multiplexed Cell Paint assay labeling the nucleus, cell membrane, actin, endoplasmic reticulum, Golgi apparatus, and mitochondria. Each flow cell included 12 replicate wells, which exhibited highly consistent profiles with minimal variability across replicates. Across ~140,000 cells, we profiled the expression of 50 protein targets, with an average of >100 counts per cell. Comparative analysis identifies differential expression of at least five aging-associated markers between the two neuron types. Morphological profiling further supports distinct phenotypes, based on CellProfiler features such as MajorAxisLength, MaxFeretDiameter, and ConvexArea. These preliminary findings underscore the importance of *in vitro* model selection and favor the use of

trans-differentiated neurons as a relevant model for studying age-related neurodegenerative processes.

Disclosures: D. Pant: None. T. Wolf: None. S. Lymer: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.17/C48

Topic: C.01. Brain Wellness and Aging

Title: Mapping the human cerebellum with 6-base sequencing

Authors: *T. CHARLESWORTH¹, P. CREED², J. MONAHAN², R. CRAWFORD⁴, E. LLESHI⁴, M. CONSUGAR³, L. SARRE⁴, F. PUDDU⁴;

¹biomodal, Little Chesterford, Saffron Walden, United Kingdom; ²biomodal, Cambridge, United Kingdom; ³biomodal, Arlington, MA; ⁴biomodal Ltd, Cambridge, United Kingdom

Abstract: The human brain exhibits unique epigenetic features that support its highly specialized roles in information processing, motor control, consciousness, learning, and memory. In particular, 5-hydroxymethylcytosine, also known as the sixth DNA base of the genome, is known to be significantly enriched in many cells found in brain tissue. Here, we apply 6-base sequencing, an assay capable of simultaneously detecting all four canonical DNA bases along with two key epigenetic modifications—5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC)—to comprehensively profile the cerebellar epigenome. We generated a high-resolution 5-methylome and 5-hydroxymethylome profile from post-mortem human cerebellum and compared this to profiles from a panel of non-brain tissues, including liver, lung, and breast. Our analysis reveals that the cerebellum harbors a distinct epigenetic signature characterized by widespread 5hmC enrichment at neuronal gene bodies and enhancer regions, consistent with active transcriptional regulation. These findings demonstrate the power of 6-base sequencing to resolve tissue-specific epigenetic landscapes and underscore the cerebellum's unique regulatory architecture. This approach provides a valuable framework for understanding brain-specific gene regulation and its disruption in neurological disease.

Disclosures: T. Charlesworth: None. P. Creed: None. J. Monahan: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.18/C49

Topic: C.01. Brain Wellness and Aging

Support: INBRE

Title: The impact of aging on the sympathetic nervous system: alteration of adrenergic receptors

Authors: *C. D. FRANCIA, L. DE LA CRUZ;
Biol., Idaho State Univ., Pocatello, ID

Abstract: The autonomic nervous system consists of the sympathetic and parasympathetic nervous system. These systems are key regulators of glucose metabolism through the regulation of hormone secretion, such as insulin and glucagon. Particularly, aging has been associated with sympathetic nervous system dysfunction, and it's linked to organ functional decline, as observed in the heart. However, whether age-associated sympathetic system dysfunction impacts insulin and glucagon secretion, thereby increasing the risk of developing metabolic disease, is poorly understood. The role of the sympathetic nervous system in regulating insulin secretion is mediated by adrenergic receptor activation in both insulin-releasing beta-cells (β -cells) and the pericyte-vessel complex. Based on this, the goal of our research is to investigate whether aging induces changes in the expression, localization, and function of adrenergic receptors in β -cells and the pericyte-vessel complex using 3D modeling. Alterations in the adrenergic receptors are expected to impair the sympathetic nervous system and the pancreas, thereby affecting hormone release. Pancreas tissue was collected from female and male C57BL/6 mice; the ages considered were young (4-5 months old) and old (25-28 months old). Immunohistochemistry staining of pancreas slices of 300 μ m was conducted to identify α 2 and β 2 adrenergic receptors and insulin (to mark the pancreatic islet area in the pancreas). After staining, tissue clearing was performed using ethyl cinnamate to render the tissue transparent and provide access to intact islets within the tissue. Images were taken using confocal microscopy. ImageJ software was used for image analysis, and IMARIS software was used to create 3D imaging. Our preliminary data show that both α 2 and β 2 receptors are expressed within the pancreatic islet. α 2 are observed in β -cells, with stronger expression in the nuclei, and, interestingly, are also observed in non-positive insulin cells, most likely α cells. This expression pattern of α 2 receptors remains consistent across ages and sexes. The β 2 receptor, expressed within the pancreatic islet, exhibits a strong signal in both β -cells and some insulin-negative cells located in the periphery of the islet, consistent across both sexes. The expression of the β 2 receptor is also observed near blood vessels within the islet in young animals, but it shows increased expression near vessels in old age. This age-related increase in β 2 receptors near vessels suggests a potential alteration in the sympathetic regulation of the islet's pericytes-vessel complex, influencing changes in insulin secretion through blood flow changes.

Disclosures: C.D. Francia: None. L. de la Cruz: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.19/C50

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 1U01MH121260-01

Title: Cellular and molecular signatures of sex-specific aging in the primate brain

Authors: *K. WATKINS¹, W. YANG³, A. DECASIEN⁵, M. O'NEILL⁶, M. O. BOHLEN⁷, L. STARITA⁶, M. J. MONTAGUE⁸, M. L. PLATT⁹, K. CHIOU¹⁰, J. SHENDURE⁴, N. SNYDER-MACKLER²;

¹Ctr. for Evolution & Med., ²Sch. of Life Sci., Arizona State Univ., Tempe, AZ; ⁴Genome Sci.,

³Univ. of Washington, Seattle, WA; ⁵NIH, Bethesda, MD; ⁶Brotman Baty Inst., Seattle, WA;

⁷Biomed. Engin., Duke Univ. Neurobio. Grad. Program, Durham, NC; ⁸Neurosci.,

⁹Neuroscience, Perelman Sch. of Med., Univ. of Pennsylvania, Philadelphia, PA; ¹⁰Biol., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Neurodegenerative disorder risk increases with age but differentially by sex, yet the underlying molecular mechanisms remain poorly understood. Uncovering these mechanisms in humans is constrained by the difficulty of obtaining intact brain samples across the lifespan that permit high-resolution multi-omic investigation. Here, we turned to rhesus macaques, which exhibit similar neuroanatomy and age-related changes as humans. We performed single nucleus RNA-sequencing on 5.3 million nuclei, sampled across 11 brain regions from 55 rhesus macaque donors (29 female, 26 male), ranging in age from 0.4 to 20.8 years. Overall, we found that 9380 (62%) unique genes show differential expression as a function of age in at least one region or cell type, and 8748 (58%) show sex differences in expression (local false sign rate, LFSR<0.05). We looked at the intersection of sex- and age-associated genes (a+sDEGs) within each cell cluster and region, and found 4629 unique a+sDEGs. We classified these as either “female-older”, where the effect of being female amplified aging effects, or “male-older” where the effect of being male amplified aging effects on gene expression in each subcluster-region. Analysis revealed 34% of subtype-region combinations showed female-older patterns versus 7% male-older patterns (FDR<0.05). We observed a female-older bias in a+sDEG proportions across all regions in astrocytes, microglia, oligodendrocytes, as well as cerebellar, GABAergic, glutamatergic, and midbrain neurons. Although male-older a+sDEG expression was less common, we identified a striking pattern of male-older expression in medium spiny neurons (MSNs) in the nucleus accumbens (NAc). The a+sDEGs in this subpopulation were upregulated with age, and enriched for genes associated with lipid metabolism and catabolism. Sex differences in gene expression here may contribute to greater susceptibility of NAc MSNs to pathological insults, such as those associated with Parkinson’s disease, a neurodegenerative disorder more prevalent in men. We also identified sex differences in age-associated downregulation of genes associated with synaptic function in astrocytes and oligodendrocytes: synapse-associated genes in astrocytes show lower expression in females, while a different set of synapse-associated genes in oligodendrocytes show lower expression in males. These sex-specific aging patterns may inform precision approaches to neurodegeneration and provide a high-resolution primate brain atlas for continued translational research.

Disclosures: K. Watkins: None. W. Yang: None. A. DeCasien: None. M. O'Neill: None. M.O. Bohlen: None. L. Starita: None. M.J. Montague: None. M.L. Platt: None. K. Chiou: None. J. Shendure: None. N. Snyder-Mackler: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.20/C51

Topic: C.01. Brain Wellness and Aging

Title: From mental to mechanical stress through Lamin B1 in the Dentate Gyrus

Authors: *K. MICHEL¹, S. THURET³, T. TODA²;

¹Max-Planck Ctr. for Physics and Med., Fürth, Germany; ²Max-Planck Ctr. for Physics and Med., Erlangen, Germany; ³Dept. of Basic and Clin. Neurosci., Kings Col. London, London, United Kingdom

Abstract: Brains adapt their structure and function to environmental changes or pathology. These changes range from the tissue to the cellular level, although their interplay remains largely elusive. For instance, in major depressive disorder (MDD), the dentate gyrus (DG) of the hippocampus shrinks at onset but recovers after therapy, despite unchanged cell numbers, implying structural dynamics drive brain resilience alongside cellular signaling. To address this knowledge gap, we investigated how chronic stress, a major MDD risk factor, reshapes DG architecture and its neurogenic niche in the mouse hippocampus. We developed an imaging pipeline to quantify nuclear shape alongside local tissue topology. We found that nuclei in DG were shrunk and local tissue topology became more constricted after chronic stress, which likely contributes to limited integration and migration of neural progenitor cells (NPCs) in DG. At the cellular level, chronic stress-related signals reduced lamin B1 levels, a key nuclear structural protein, resulting in altered NPC nuclear mechanics as measured by AFM and Brillouin microscopy. Lamin B1 knockout recapitulated stress-induced mis-migration and changes in nuclear mechanics. These findings highlight lamin B1 as a crucial mechanistic link between chronic stress and structural plasticity of the DG from the cellular to tissue level.

Disclosures: K. Michel: None. S. Thuret: None. T. Toda: None.

Poster

PSTR010: Spatial Mapping of Brain Changes in Aging

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR010.21/C52

Topic: C.01. Brain Wellness and Aging

Title: Investigating brain-region-specific and time-dependent ferroptosis after single administration of SARS-CoV-2 spike protein

Authors: *O. A. ABULSEOUD¹, A. HATEM²;

¹Mayo Clin., Phoenix, AZ; ²Dept. of Neuroscience, Grad. Sch. of Biomed. Sciences, Mayo Clin. Col. of Medicine, Phoenix, Arizona, Scottsdale, AZ

Abstract: Post-COVID syndrome, post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID all refer to a group of neurological, cognitive, and psychiatric manifestations that persist for more than 12 weeks after recovery from acute SARS-CoV-2 infection, regardless of illness severity, and cannot be explained by an alternative diagnosis. However, the enigmatic nature of the pathophysiology makes both diagnosis and management complicated. Iron dysregulation, oxidative stress and lipid peroxidation markers have been repeatedly reported in COVID-19 patients. These three items comprise the hallmarks of ferroptosis, an iron-dependent programmed cell death. Ferroptosis is reported as a part of the pathogenesis of multiple neuropsychiatric disorders. The SARS-CoV-2 spike protein is claimed to be responsible for some of the post-COVID manifestations. Therefore, we aimed to investigate the SARS-CoV-2 spike protein-induced ferroptosis. We administered 600ug/kg intranasal SARS-CoV-2 spike protein (S1) to male K18h ACE2 transgenic mice. We tested five ferroptosis related markers by western blotting (Transferrin receptor1 (TFR1), Ferroportin 1 (FPN1), divalent metal transporter (DMT1), glutathione peroxidase 4 (GPX4), and nuclear factor erythroid 2-related factor 2 (Nrf2)) in olfactory bulb, prefrontal cortex, hippocampus, and cerebellum. We investigated these markers at three time points (2-, 6-, and 12-weeks) after SARS-CoV-2 spike protein administration. We detected a significant increase in TFR1 in the 2-week olfactory bulb, 6-week hippocampus, and 2-week cerebellum in spike-treated mice compared to controls. FPN1 was also significantly increased in the 12-week olfactory bulb, 2-week prefrontal cortex, 2-week cerebellum, and 2-week hippocampus. Notably, FPN1 showed a significant decrease in the 6-week hippocampus in spike-treated mice compared to controls. DMT1 showed a significant increase in the 2-week prefrontal cortex and the 12-week cerebellum. Despite the significantly increased expression of GPX4 in the 6-week prefrontal cortex and the 2-week cerebellum, it was reduced in the 2-week olfactory bulb. Nrf2 showed a significant increase only in the 6-week hippocampus. In addition, we ran transmission electron microscopy to detect ferroptotic features of cells. The prefrontal cortex showed cells with extremely electron-lucent cytoplasm and nucleus and breaks in the cell plasma membrane. Our results denote brain-specific and time-dependent alterations in ferroptosis-related markers.

Disclosures: O.A. Abulseoud: None. A. Hatem: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.01/C53

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

Support: NIH_RO1_AG073826-01A1

Title: Kcnp1 at the convergence of retinoic acid receptor regulation, ion channel dysfunction, and alzheimer's disease: a bioinformatics study

Authors: *N. KHANNA^{1,2,4,5}, F. K. TSURUKAWA³, C. SANCHEZ VILLALOBOS³, I. CASTRO-PIEDRAS², C. BOSE^{5,6}, R. PAL³, C. J. CRASTO², J. J. LAWRENCE^{5,4,6,7};
¹Texas Tech. Univ. Hlth. sciences Ctr., Lubbock, TX; ²Ctr. For Biotech. and Genomics,
³Electrical and Computer Engin., Texas Tech. Univ., Lubbock, TX; ⁴Ctr. of Excellence in
Translational Neurosci. and Therapeut., ⁵Dept. of Pharmacol. and Neurosci., ⁶Garrison Inst. on
Aging, ⁷Ctr. of Excellence for Integrative Hlth., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Our previous study (Tsurukawa et al. 2025) highlights the significant advantage of multivariate machine learning approaches in capturing complex gene interactions in human Alzheimer's disease (AD). The integrative analysis of three independent postmortem human hippocampal transcriptomic datasets identified KCNIP1 consistently achieving top aggregate scores in our bivariate ranking methodology across all datasets. KCNIP1, nominated as an AD gene in 2018 (Agora), is an interacting protein that regulates the trafficking of Kv4.1 ion channels to the membrane. Kim et al. (2021) demonstrated that Kv4.1 levels are reduced in an AD mouse model, which is associated with the hyperexcitability of dentate gyrus granule cells (DGGCs). Indeed, hyperexcitability of the hippocampal dentate gyrus (DG) is associated with impaired learning in the early stages of human Alzheimer's disease (AD). Converging evidence also suggests that all-trans retinoic acid (ATRA) deficiency in AD disrupts cellular homeostasis. Here, we determined the extent to which KCNIP1 is a retinoic acid receptor (RAR)-sensitive gene by identifying retinoic acid response elements (RAREs) in its promoter region. Our bioinformatics workflow utilized a strategic combination of computational platforms, including Enrichr, tf2DNA, JASPAR, and MEME Suite, to analyze transcription factor binding site (TFBS) regulatory elements. We systematically analyzed and evaluated TFBSs in the full-length promoter regions of both the human and mouse KCNIP1 genes that exceeded the binding affinity threshold. This analysis identified 100 putative RARE TFBS in the human KCNIP1 gene, with the top 20 JASPAR abundance scores (AS) of 13.87 ± 1.47 (mean $\pm$ SD). Mouse KCNIP1 had 77 RARE TFBSs with an AS of 11.77 ± 0.34 . A comparison of these human and mouse AS scores revealed significantly higher AS in the human KCNIP1 promoter than in the mouse ($F(19.14, 19)$; $p < 0.0001$, unpaired t-test). JASPAR relative scores, which indicate the relative strength of TFBSs, were also significant (human: 0.86 ± 0.029 , mouse: 0.83 ± 0.007 , $F(14.96, 19)$, $p < 0.0001$), suggesting increased sensitivity of KCNIP1 expression by RAR signaling in human AD. In conclusion, we have revealed a novel nutrigenomics-based molecular mechanism connecting RAR dysregulation to DG hyperexcitability. We speculate that ATRA deficiency reduces KCNIP1 expression, which reduces surface expression of Kv4.1 potassium channels, leading to hyperexcitability of DGGCs. Future studies are needed to provide further support for this plausible mechanism. This novel TFBS analysis can be extended to other key AD genes for studying species-specific regulatory mechanisms.

Disclosures: N. Khanna: None. F.K. Tsurukawa: None. C. Sanchez Villalobos: None. I. Castro-Piedras: None. C. bose: None. R. Pal: None. C.J. Crasto: None. J.J. Lawrence: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.02/C54

Topic: C.06. Neuromuscular Diseases

Support: DOD Grant W81XWH2010028
AHA Grant 23CDA1046074
NIH Grant R01 HG012573
NIH Grant K01 AG051791
Suh Kyungbae Foundation Grant
NIH Grant DP2 AG072437
NIH Grant R01 NS032457

Title: Recurrent patterns of widespread neuronal genomic damage shared by major neurodegenerative disorders

Authors: *Z. ZHOU¹, L. LUQUETTE², G. DONG³, P. PARK², C. LAGIER-TOURENNE⁴, E. LEE⁵, C. A. WALSH³;

¹Genet. and Genomics, Boston Children's Hospital/Harvard Med. Sch., Boston, MA; ²Dept. of Biomed. Informatics, Harvard Med. Sch., Boston, MA; ³Genet. and Genomics, Boston Children's Hosp., Boston, MA; ⁴Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; ⁵Genet. and Genomics, Boston Children's Hospital, Harvard Med. Sch., Boston, MA

Abstract: Amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD) belong to two major categories of neurodegenerative disorders—TDP-43 and tau proteinopathies—for which the mechanisms driving neuronal death remain unclear. Single-cell whole-genome sequencing of 429 neurons from three *C9ORF72* ALS, six *C9ORF72* FTD, seven AD, and twenty-three neurotypical control brains revealed significantly increased burdens in somatic single nucleotide variant (sSNV) and insertion/deletion (sIndel) in all three disease conditions. Mutational signature analysis identified a disease-associated sSNV signature suggestive of oxidative damage and an sIndel process, affecting 28% of ALS, 79% of FTD, and 65% of AD neurons but only 5% of control neurons (diseased vs. control: OR = 31.20, $p = 2.35 \times 10^{-10}$). Disease-associated sIndels were primarily two-basepair deletions resembling Catalogue of Somatic Mutations in Cancer (COSMIC) signature ID4, which was previously linked to topoisomerase 1 (TOP1)-mediated ribonucleotide excision repair. Duplex sequencing confirmed the presence of sIndels and identified similar single-strand events as potential precursor lesions. Consistent with TOP1-mediated mutagenesis, we identified hallmark features of TOP1-mediated Indels, including a local TNT motif at the deletion site, preferential deletion of the CT dinucleotide, and a correlation with local gene expression levels. In addition, diseased neurons exhibited reduced expression of genes that maintain the balance of free rNTP and dNTP pools and participate in rNTP removal from genomic DNA, both of which may trigger TOP1 recruitment and subsequent mutagenesis. Our results suggest that TOP1-associated sIndel

mutagenesis and resulting genome instability may thus represent a common mechanism of neurodegeneration shared by both TDP-43 and tau proteinopathies.

Disclosures: **Z. Zhou:** None. **L. Luquette:** None. **G. Dong:** None. **P. Park:** F. Consulting Fees (e.g., advisory boards); P.J.P. is a member of the scientific advisory board for Bioskryb Genomics, Inc. **C. Lagier-Tourenne:** F. Consulting Fees (e.g., advisory boards); C.L.-T serves on the scientific advisory board of SOLA Biosciences, Libra Therapeutics, Arbor Biotechnologies and Dewpoint Therapeutics and has received consultant fees from Mitsubishi Tanabe Pharma H. **E. Lee:** F. Consulting Fees (e.g., advisory boards); E.A.L. serves on the scientific advisory board of Genome Insight. **C.A. Walsh:** F. Consulting Fees (e.g., advisory boards); C.A.W. is a paid consultant (cash, no equity) to Third Rock Ventures and Flagship Pioneering (cash, no equity) and is on the Clinical Advisory Board (cash and equity) of Maze Therapeutics..

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.03/C55

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

Support: Autism Science Foundation Predoctoral Fellowship
NIMH F31 MH138112
NIH K01MH116098
NIH R01MH132746
NIH P30 AG072980
Arizona Biomedical Research Commission ADHS16-162413
Department of Defense W81XWH-15-1-0211

Title: Alzheimer's disease genetic risk dosage in autistic individuals

Authors: ***S. A. HARKER**¹, I. S. PIRAS⁵, F. TAGUINOD⁶, M. J. HUENTELMAN⁵, R. CASTRO¹, H. CERVANTES², L. RUHTER², E. STEIN², B. BRADEN³, C. R. LEWIS⁴;
¹Arizona State Univ., Tempe, AZ; ³Dept. of Speech and Hearing Sci., ⁴SOLS, ²Arizona State Univ., Phoenix, AZ; ⁵Neurogenomics, ⁶TGen, Phoenix, AZ

Abstract: Older adults with autism spectrum disorder (ASD) are 18 times more likely to be diagnosed with Alzheimer's disease (AD) compared to neurotypical (NT) adults. Despite known lifelong challenges, understanding of cognitive and brain aging with autism is lacking. Genetics, such as apolipoprotein E (*APOE*) allele 4 ($\epsilon 4$), explain substantial variance in cognitive aging and incidence of neurodegenerative disease. Polygenic Scores (PGS) are an effective tool used to generate a genomic risk dosage for various conditions and diseases, like AD. In this study, we hypothesize that 1) Autistic adults will have accelerated decline in cognitive functions most vulnerable to AD, long-term memory, in comparison to NT, 2) *APOE* $\epsilon 4$ -allele will have a

greater negative impact on autistic adult's long-term memory, compared to NT adults, and 3) Autistic adults carry a higher cumulative genetic risk for AD, compared to NT adults. Long-Term Memory: A total of 87 participants (ASD n=45; NT n=42) completed the Auditory Verbal Learning Test Delayed Recall (AVLT A7) with up to five timepoints (Mean = 2.5 years (± 2.5); Range = 0-9 years). Multilevel modeling was conducted in R with the lme4 package to evaluate the main effect of autism on AVLT A7 over time and the interaction. *APOE*: A total of 156 participants (ASD n=91; NT n=75) consented to provide saliva samples for *APOE* genotyping. AD-PGS: A total of 119 participants (ASD n=67; NT n=52) consented to provide saliva samples for microarray analysis. AD-PGS was generated via PRS-continuous shrinkage (PRS-CS) using an AD genome wide association study of 71,880 AD cases and 383,378 controls. There was a significant interaction between time and diagnosis group (Autism vs. NT) for long-term verbal memory, with the autism group demonstrating steeper memory decline over time. Controlling for $\epsilon 4$ carrier status and sex, autistic adults performed significantly worse on long-term verbal memory. Autistic male $\epsilon 4$ carriers had worse performance on long-term memory compared to autistic female $\epsilon 4$ carriers. NT male $\epsilon 4$ carriers performed worse on long-term memory, compared to NT female $\epsilon 4$ carriers. Autistic individuals had significantly greater AD-PGS (higher AD risk) than NT, controlling for the interaction with sex and ancestry ($p=0.03295$). Autistic adults show accelerated long-term memory decline, compared to NT. The *APOE* $\epsilon 4$ -allele may have the greatest negative impact on autistic and NT men's memory, compared to autistic and NT females. Autistic adults, show greater cumulative genetic risk for AD, compared to NT. Taken together, these results suggest that ASD individuals may have impaired cognitive aging partially driven by AD-related genetic risk.

Disclosures: S.A. Harker: None. I.S. Piras: None. F. Taguinod: None. M.J. Huentelman: None. R. Castro: None. H. Cervantes: None. L. Ruhter: None. E. Stein: None. B. Braden: None. C.R. Lewis: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.04/C56

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

Support: NIH Grant U19 AG074866
NIH Grant R24 AG073190

Title: Genetic association of neurodegeneration biomarkers in a population of laboratory marmosets

Authors: *G. W. CARTER¹, D. SZCZUPAK², H. HUHE⁶, T. MURAI⁷, S.-H. CHOI³, J. PARK³, L. BAILEY³, L. SCHAEFFER⁴, A. C. SILVA⁵, S. J. SUKOFF RIZZO⁸;

¹The Jackson Lab., Bar Harbor, ME; ²Neurobio., ³Univ. of Pittsburgh, Pittsburgh, PA;

⁴Neurobio., Univ. of Pittsburgh, Monroeville, PA; ⁵Dept. of Neurobio., Univ. of Pittsburgh,

Pittsburgh, PA; ⁶Dept. of medicine, ⁷Aging Inst., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; ⁸Dept. of Med., Univ. of Pittsburgh Sch. of Med., PITTSBURGH, PA

Abstract: Background: Alzheimer's disease is the most common form of dementia and will likely require early intervention for effective treatment. Its gradual progression and the inaccessibility of middle-aged brain tissue has limited the discovery of therapeutic strategies. The need for in vivo systems to study the origins of biological dysfunction motivates establishment of new model systems with age-related molecular, imaging, and behavioral changes. Here, we report genetic factors influencing plasma and imaging biomarkers related to Alzheimer's disease in the common marmoset.

Methods: We have performed whole-genome sequencing, plasma biomarkers, and in vivo neuroimaging on over 220 individual marmosets, including genetically engineered carriers of rare human variants of *PSEN1*. DNA was obtained from fibroblast cultures and short-read sequences were aligned to a recently-completed telomere-to-telomere reference assembly. Plasma biomarkers including A β 40, A β 42, and total Tau and imaging metrics from the same animals were mapped for genetic effects using PermGWAS2 software, which combines a linear mixed model to address kinship and a permutation test to establish false discovery thresholds.

Results: We found weak associations between age and plasma biomarkers, suggesting the potential for significant genetic contributions to population-level variation. Genome scans revealed a significant association locus for corpus callosum volume and loci associated with plasma biomarkers. Candidate regions often overlapped with human GWAS loci for dementias and/or contained genes with transcript or protein associations with Alzheimer's disease in postmortem human brains.

Conclusions: These early genetic results are a foundation for additional lifespan studies to determine how dementias initiate and progress in a non-human primate model. Our study provides a roadmap for deep molecular analysis of aging marmosets as a model of dementia.

Disclosures: G.W. Carter: None. D. Szczupak: None. H. Huhe: None. T. Murai: None. S. Choi: None. J. Park: None. L. Bailey: None. L. Schaeffer: None. A.C. Silva: None. S.J. Sukoff Rizzo: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.05/C57

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

Title: Uncovering Serum Exosomal miRNA Signatures in Alzheimer's Disease

Authors: *Y. CHO, Y. CHO, D.-G. JO;
Sch. of Pharm., Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide, characterized by progressive cognitive decline. The apolipoprotein E (APOE) gene is the strongest genetic risk factor for late-onset AD (LOAD). In humans, APOE exists in three major isoforms—APOE2, APOE3, and APOE4—with APOE4 increasing disease susceptibility and APOE2 generally considered protective. Exosomes, small extracellular vesicles ranging from 40 to 160 nm in diameter, carry various molecular cargos including proteins, nucleic acids, and non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). These vesicles have garnered attention for their role in intercellular communication and their potential utility as biomarkers. In this study, serum-derived exosomes were isolated from individuals with different APOE genotypes. Using next-generation sequencing, we compared small RNA profiles between cognitively unimpaired (CU) and cognitively impaired (CI) individuals within each genotype group to investigate genotype-specific associations with cognitive status. These findings suggest that serum exosomal RNAs may reflect genotype-dependent molecular alterations associated with AD progression. Such profiles may provide insight into the molecular heterogeneity of AD and serve as a basis for future investigations into disease mechanisms, progression, and therapeutic targets.

Disclosures: Y. Cho: None. Y. Cho: None. D. Jo: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.06/C58

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

Support: NIA- P30AG10133, P30AG072976
R56AG072810
R21AG056007
R21AG074539
R21AG076202

Title: Mechanistic insight into microRNA-153's target- and cell-type specific regulation and its neurobiological Implications

Authors: *D. K. LAHIRI^{1,6}, R. WANG¹, B. MALONEY^{1,6}, M. JUBOORI¹, F. A. WHITE², K. NHO^{3,6}, A. J. SAYKIN^{3,6}, M. R. FARLOW^{4,6}, K. L. NEWELL^{5,6}, B. GHETTI^{5,6}, J. T. ROGERS⁷, K. SAMBAMURTI⁸, N. GREIG⁹, J. M. LONG^{10,11}, S. E. COUNTS^{12,13};

¹Psychiatry, ²Anesthesia, ³Radiology & Imaging Sci., ⁴Neurol., ⁵Pathology & Lab. Med., Indiana Univ. Sch. of Med., Indianapolis, IN; ⁶Indiana ADRC, Indianapolis, IN; ⁷Mass Gen Hosp Genet. & Age Res. Unit, Charlestown, MA; ⁸Neurosciences, Med. Univ. of South Carolina (MUSC), Charleston, SC; ⁹Translational Gerontology Br, Natl. Inst. on Aging, NIH, Baltimore, MD; ¹⁰Neurol., Washington Univ. Sch. of Med. In St Lou, Saint Louis, MO; ¹¹Knight ADRC, Saint

Louis, MO; ¹²Transl Sci. and Mol Med, Family Med., Michigan State Univ., Grand Rapids, MI;
¹³Michigan ADRC, Grand Rapids, MI

Abstract: Alzheimer's disease (AD) is characterized by neurofibrillary tangles, primarily composed of hyperphosphorylated tau, a microtubule-associated protein; senile plaques, composed of amyloid β (A β) peptides; and neuroinflammation. Genetic and environmental factors play important roles in disease progression. MicroRNAs (miRNAs), a group of small non-coding RNAs, regulate biological pathways by binding to target messenger RNAs (mRNAs) and altering their translation levels. Disrupting this process could contribute to AD pathogenesis. We have reported that human miRNA-153-3p (miR153) inhibits the expression of APP, the repressor element 1 silencing transcription factor (REST), and α -synuclein (SNCA), and promotes neuronal differentiation. Regulation by miRNAs could be influenced by target mRNA 3' untranslated region (UTR) truncation or alteration. Herein, we report that elevated miR153 leads to apoptosis, potentially via REST knockdown, in specific cell types and its implications in AD. We first performed real-time qPCR to determine miR153 levels in human autopsied brain tissue samples from AD and non-demented subjects. We observed that miR153 elevation was associated with a reduced likelihood of AD. The cell-type-specific regulation and mechanisms that link miR153 activity to AD risk are unknown. Therefore, we performed a second set of experiments using miRNA transfection in human epithelial, astrocytic, microglial, and neuronal cell lines, with either a mock, miR-153 mimic, antagomiR, both a mimic and antagomiR, or a negative control. miR153 treatment significantly decreased the expression of REST, SNCA, and APP proteins. Unlike in neuronal cells, miR153 treatment led to apoptosis and cell death, as indicated by increased cleaved caspase-3, 7, and 9, and PARP alongside reduced CTG in non-neuronal cells. We have previously shown that 3' UTR binding sites for miRNAs can be altered between neuronal and non-neuronal cell types. Hence, the non-neuronal induction of apoptosis could be due to REST knockdown and/or to cell type-specific alterations in the target mRNA 3' UTR. Furthermore, MIR153 genes and their single-nucleotide polymorphisms (SNPs) are associated with at least two AD-related endophenotypes that may serve as potential disease biomarkers. Altogether, miR153-induced apoptosis in non-neuronal cells, coupled with miR153's ability to promote neuronal differentiation, could play a crucial role in neuronal development, and its dysregulation could contribute to AD pathogenesis. Supported by NIA/NIH grants.

Disclosures: D.K. Lahiri: None. R. Wang: None. B. Maloney: None. M. Juboori: None. F.A. White: None. K. Nho: None. A.J. Saykin: None. M.R. Farlow: None. K.L. Newell: None. B. Ghetti: None. J.T. Rogers: None. K. Sambamurti: None. N. Greig: None. J.M. Long: None. S.E. Counts: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.07/C59

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

Support: F32AG090054 (MT)
Emory ADRC P30AG066511 (MT)
RF1AG79199 (DW)
R01AG062581 (DW)

Title: Developing human locus coeruleus organoids to study regional selective vulnerability in Alzheimer's disease

Authors: *M. TISH, Y. GAO, Z. OU, F. BIREY, D. WEINSHENKER;
Dept. of Human Genet., Emory Univ., Atlanta, GA

Abstract: The brainstem locus coeruleus (LC), is the first brain region to develop hyperphosphorylated tau (ptau) inclusions in Alzheimer's disease (AD) and undergoes catastrophic degeneration starting in mid-stage disease. The LC is the main noradrenergic nucleus and source of norepinephrine (NE) in the forebrain. Dysregulation of LC-NE transmission is associated with both cognitive and non-cognitive AD symptoms, as its release in the forebrain regulates attention, arousal, stress response, and learning and memory. Moreover, the LC may transmit pathogenic tau to the forebrain via its extensive projections. However, nearly all information about the LC in AD has been derived from rodent models and postmortem or human imaging studies. It is not known how the early ptau accumulation in the human LC affects neuronal function, NE transmission, or pathology propagation. We created organoids, which are 3D human cell culture models derived from human induced pluripotent stem cells, to model the human LC. Organoids were generated from human induced pluripotent stem cells using growth factors that induce a hindbrain fate. These organoids were then characterized using HPLC, immunohistochemistry, RNA-scope and RNA-sequencing. Human cortical organoids were used for comparison. LC organoids contained higher levels of NE and dopamine than cortical organoids. They also expressed neuromelanin-like pigment and many of the proteins and mRNAs that are indicative of and enriched in LC-NE neurons, including tyrosine hydroxylase, dopamine beta-hydroxylase, the NE transporter, Phox2A, and Phox2B. Additionally, bulk RNA-seq revealed that compared to cortical organoids, the LC organoid transcriptome more closely resembled the human LC. After creating organoids that possess noradrenergic neurons and many aspects of the human LC, we have started creating LC organoids from stem cells of patients with familial AD. Studying the structure and function of LC organoids derived from both healthy controls and AD patients may provide new insights into the role of the LC and biology of selective vulnerability in AD.

Disclosures: M. Tish: None. Y. Gao: None. Z. Ou: None. F. Birey: None. D. Weinshenker: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.08/C60

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

Support: NIH RF1 AG81203
NIH U19 AG69701

Title: Impact of ABCA7 deficiency in glia-enriched iPSC cortical organoids

Authors: ***T. NAMBARA**, G. OMANA SUAREZ, N. WANG, T. KANEKIYO;
Neurosci., Mayo Clin., Jacksonville, FL

Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disease influenced by various genetic and environmental factors. Among identified genetic risk factors, the *ABCA7* gene encoding ATP-binding cassette (ABC) subfamily A member 7 stands out as a significant contributor to the pathogenesis of AD. Loss-of-function mutations in *ABCA7* are linked to an increased risk of developing AD. ABC transporters play a key role in lipid balance and regulate substances critical for neuronal health. While our previous research found that ABCA7 deficiency disrupts neuronal mitochondrial lipid metabolism, ABCA7 is also expressed in astrocytes, glial cells essential for supporting neuronal integrity. To investigate the role of *ABCA7* in glial cells, we generated glia-enriched cortical organoids that exhibit accelerated gliogenesis to further investigate the role of *ABCA7* in glial cells using ABCA7 knockout (KO) and isogenic control induced pluripotent stem cell (iPSC) lines. After 6 months of differentiation for the iPSC-derived embryoid bodies (EBs), single-cell RNA sequencing (scRNA-seq) was performed in the organoids. We identified 12 distinct clusters, including not only glutamatergic and GABAergic neurons but also astrocytes, immature astrocytes, astrocyte progenitor cells, oligodendrocyte precursor cells, and oligodendrocytes. Among these, a large proportion of these clusters were associated with astrocyte-related populations. In the mature astrocyte cluster, pathways related to aerobic respiration, metabolites and energy metabolism, and the regulation of synapse organization were significantly altered. The mature astrocyte cluster showed the upregulation of pathways involved in protein folding and chaperone-mediated protein processing, alongside downregulation of synapse assembly. In the glutamatergic neuron cluster, the downregulation of pathways associated with synapse organization was observed. Our study demonstrated that ABCA7 deficiency affects the gene signatures of both neurons and astrocytes in the iPSC-derived organoids. These alterations may have a significant impact on the neurodegenerative processes observed in AD. Exploring impacts of ABCA7 deficiency in specific cell types could provide a clue to develop novel therapeutic strategies for AD.

Disclosures: **T. Nambara:** None. **G. Omana Suarez:** None. **N. Wang:** None. **T. Kanekiyo:** None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.09/C61

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

Support: NIH Grant K99AG065511
NIH Grant R00AG065511
NIH Grant R01AG093746
McJunkin Family Foundation
McKnight Brain Institute

Title: Studying the role of CASP8 GGGAGA repeat expansion in Alzheimer's disease

Authors: *A. SUAREZ¹, B. HYMAN², L. NGUYEN³;

¹Univ. of Florida, Gainesville, FL; ²Neurol., Massachusetts Gen. Hosp., madison, NH; ³Ctr. For Neurogenetics, Mol. Genet. and Microbiology, Univ. of Florida, Gainesville, FL

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. While various genetic mutations contribute to AD risk, the complete genetic landscape remains unclear. Tandem repeat expansion mutations have been implicated in multiple neurodegenerative disorders. Recently, a repeat expansion variant in **CASP8** (CASP8-GGGAGA-AD-R1) was linked to increased AD risk (odds ratio = 2.2; $p = 3.1 \times 10^{-5}$), prompting investigation into its role in AD pathogenesis. We developed induced pluripotent stem cell (iPSC) models from AD patients with and without the CASP8-GGGAGA-AD-R1 variant, as well as from controls, to explore CASP8-related pathogenic pathways. Additionally, we engineered CRISPR/Cas9 systems to excise the CASP8-GGGAGA-AD-R1 sequence, generating isogenic lines. Neuronal cultures from these parental and isogenic iPSCs will be analyzed for disease-relevant molecular and phenotypic features. iPSCs were generated from fibroblasts of 4 CASP8-GGGAGA-AD-R1(+) AD cases, 5 CASP8-GGGAGA-C-Var(+) AD cases, and 5 controls. All lines expressed pluripotent markers and maintained normal karyotypes. Repeat-primed PCR (RP-PCR) and long-range PCR (LR-PCR) confirmed that CASP8 GGGAGA repeat genotypes were consistent with donor fibroblasts. For genome editing, we cloned a plasmid expressing Cas9, fluorescent markers (mCherry, GFP), and guide RNAs targeting the flanking sequences of the CASP8 repeat. Editing efficiency was tested in HEK293T cells and iPSCs. Fluorescence signals were detected 17-30 hours post-transfection, confirming successful Cas9 expression. LR-PCR on genomic DNA from HEK293 cells revealed expected fragment sizes, validating accurate Cas9-mediated targeting of the repeat locus. We successfully established patient-derived models to investigate the role of CASP8-GGGAGA-AD-R1 in AD. Using CRISPR/Cas9, we efficiently excised the repeat expansion in HEK293 cells. Future work will apply this system to patient-derived neurons to determine whether removing the variant mitigates AD-associated phenotypes, offering insights into disease mechanisms and potential therapeutic strategies.

Disclosures: A. Suarez: None. B. Hyman: A. Employment/Salary (full or part-time): Massachusetts General Hospital. L. Nguyen: A. Employment/Salary (full or part-time): Center For Neurogenetics, Molecular Genetics and Microbiology, University of Florida.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.10/C62

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

Support: NIH Grant RF1AG079331

Title: The role of ABCA1 in Alzheimer's Disease

Authors: *N. STERLING¹, G. YANG¹, A. RODRIGUES¹, G. D. D. VALE⁴, J. MCDONALD⁴, K. CREASY², D. J. RADER³;

¹Translational Med. and Human Genet., ²Biobehavioral Hlth. Sci., ³Genet., Univ. of Pennsylvania, Philadelphia, PA; ⁴Ctr. for Human Nutr., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Alzheimer's Disease (AD) affects more than 7 million people and represents a growing public health crisis. AD is an incurable neurodegenerative condition characterized by progressive loss of cognitive function. Recently, AD risk has been linked to genetic factors important for lipid metabolism. Genome-wide association studies (GWAS) have discovered that variants in the *ABCA1* gene confer higher risk for developing AD. ABCA1 is an ATP-binding cassette family member protein which transports lipids across the cellular lipid bilayer in a process known as lipid efflux. ABCA1 is known to transport cholesterol with high affinity. In recent studies, loss of ABCA1 has been shown to induce pro-neuroinflammatory effects including a reduction in microglia phagocytosis. Using human induced-pluripotent stem cells (iPSCs) with CRISPR-mediated knockout of *ABCA1* (*ABCA1*^{-/-}), this research aims to elucidate the function of ABCA1 in neural cells that protects against AD pathology. Via LC-MS lipid content profiling, we compared intracellular lipid levels between Control and *ABCA1*^{-/-} iPSC-derived neural cells (iNeurons, iAstrocytes, and iMicroglia). We observed the greatest changes in neural cell Ceramide and Sphingolipid levels. Importantly, in iNeurons and iAstros, *ABCA1* deletion results in intracellular accumulation of cholesterol, consistent with the idea that removal of ABCA1 will result in loss of cholesterol efflux from cells. Interestingly, we found that lipid changes due to ABCA1 loss occur with greater significance in iAstrocytes, which may be consistent with the supportive role astrocytes play in mediating brain cholesterol and amyloid-beta (A β) synthesis. Supporting our lipidomics data in iPSC-derived neural cell types, we performed genomic analyses with protein coding genetic variants associated with increased AD risk that mimic loss of *ABCA1* function to explore association with human plasma lipidome data. This study associated reductions in species of Dihexosylceramides (Hex2Cer) and Sphingomyelins (SM) with higher AD risk. We analyzed these specific lipid species in our iPSC-derived neural cell lipidomics and found a high level of correlation where a decrease in plasma lipids from MR corresponded to an increase in the cellular level of the same lipids in iAstrocytes. This data highlights the role of ABCA1 in neural lipid homeostasis and suggests that elevated levels of certain Ceramides or Sphingolipids in human brain cells could be detrimental in ways that promote AD pathogenesis. Further research will elucidate the effects of accumulating these lipids on the function of human neural cells and their effects on metabolic pathways.

Disclosures: N. Sterling: None. G. Yang: None. A. Rodrigues: None. G.D.D. Vale: None. J. McDonald: None. K. Creasy: None. D.J. Rader: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.11/C63

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

Support: CONICET
ANPCyT

Title: A naturally occurring APP variant impairs Go protein activation and protects human neurons from A β -induced neurodegeneration

Authors: *A. G. LORENZO¹, P. MARMO², L. MORO⁴, M. LAS PEÑAS⁵, M. ANTONINO³, R. ALMIRON³, C. MORALES ARIAS², J. BUSCIGLIO⁶, M. BOLLO², M. BISBAL⁷, A. BIGNANTE³;

¹Inst. Ferreyra (INIMEC-CONICET-Universidad Nacional de Córdoba), Cordoba, Argentina;

³CIQUIBIC-CONICET-UNC, ²Inst. de Investigación Médica M y M Ferreyra (INIMEC-CONICET-Universidad Nacional de Córdoba), Cordoba, Argentina; ⁴LIAN-FLENI-CONICET, Buenos Aires, Argentina; ⁵IMBIV-CONICET- Univ. Nacional de Córdoba, Cordoba, Argentina; ⁶DEPARTMENT OF NEUROBIOLOGY AND BEHAVIOR, Univ. of California, Irvine, Irvine, CA; ⁷INIMEC-CONICET, Cordoba, Argentina

Abstract: Amyloid precursor protein (APP) is central to Alzheimer's disease (AD) pathology as the source of amyloid- β (A β). Beyond its role in A β generation, membrane-bound holo-APP binds extracellular A β and triggers neurodegeneration by activating the heterotrimeric Go protein. In cell-free systems, it was previously demonstrated that a 20-amino-acid segment from the APP intracellular domain is sufficient to activate Go, and mutation of His657/His658 (APP695 numbering) abolishes this effect. To investigate the role of these histidine residues in A β toxicity, we transfected wild-type and mutant APP constructs into rat primary hippocampal neurons. While overexpression of wild-type APP (wtAPP) promoted A β toxicity (34% reduction in viability), His657/His658 substitutions (to Gly or Pro) abolished this effect (ANOVA F(9, 144)=8.3308, p= 0.00000). Co-expression of mutant APP with wtAPP also blocked A β toxicity (ANOVA F(2, 36)=21.536, p= 0.0000), suggesting a dominant-negative mechanism. Co-transfecting APP variants together with G-alpha subunit confirmed the involvement of Go protein signaling in A β toxicity and the dominant negative effect of mutant APP. To validate these findings in human neurons, we used CRISPR-Cas9 to generate isogenic iPSC-derived neurons expressing a naturally occurring APP variant (His658Pro, M-APP) identified in an individual from the Mandinka population. Upon A β exposure, wtAPP-expressing neurons exhibited increased apoptotic nuclei and AT8-positive phosphorylated tau in the somatodendritic compartment, whereas M-APP neurons showed resistance to A β -induced degeneration (cell death ANOVA F(1, 31)=18.706, p= 0.0001; AT-8 somas ANOVA F(1, 31)= 57.870, p= 0.000). Bimolecular fluorescence complementation (BiFC) assays in N2a cells revealed no difference in APP-Go binding between wtAPP and M-APP, indicating that the His658Pro mutation impairs

downstream signaling rather than interaction. These results suggest that the M-APP variant reduces Go protein activation, conferring resistance to A β neurotoxicity, highlighting a potential therapeutic mechanism for AD intervention.

Disclosures: A.G. Lorenzo: None. P. Marmo: None. L. Moro: None. M. Las Peñas: None. M. Antonino: None. R. Almiron: None. C. Morales Arias: None. J. Busciglio: None. M. Bollo: None. M. Bisbal: None. A. Bignante: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.12/C64

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

Support: NS127403

Title: Galactosylceramidase Haploinsufficiency Accelerates Neuropathology in 5xfad Mouse Model of Alzheimer's Disease

Authors: *N. SALDIVIA, D. ZELADA, K. SABITHA, J. WHITEHAIR, A. THOMAS, S. SAMANO, R. VORUGANTI, O. LAZAROV, E. R. BONGARZONE;
Univ. of Illinois at Chicago, Chicago, IL

Abstract: Lysosomal Storage Diseases (LSDs) are inherited metabolic disorders that primarily affect infants due to deficiencies in lysosomal enzymes, leading to toxic substrate accumulation. Although heterozygous carriers of LSD-related mutations have traditionally been considered asymptomatic, emerging evidence suggests that partial loss of lysosomal function may contribute to vulnerability to adult-onset neurodegenerative diseases. In this study, we investigate the role of galactosylceramidase (GALC)—the lysosomal enzyme deficient in Krabbe Disease (KD)—in modulating Alzheimer disease (AD) pathology. To test this, we generated a novel GALC haploinsufficient 5xFAD mouse model and evaluated cognitive and neuropathological outcomes. Behavioral performance was assessed using the Novel Object Recognition (NOR) test at multiple time points. Brain tissues were analyzed for neuroinflammation, astrogliosis, microgliosis, A β deposition, and associated biochemical markers. Our results show that GALC haploinsufficiency significantly exacerbates hallmark features of AD, including early cognitive decline, increased A β plaque burden, and heightened gliosis. These findings challenge the assumption that carriers of LSD-related mutations are unaffected and reveal a previously unrecognized role for lysosomal enzyme activity in modulating the progression of neurodegenerative disease. Our data position GALC as a novel genetic modifier of AD pathology and underscore the broader relevance of lysosomal function in adult brain vulnerability.

Disclosures: N. Saldivia: None. D. Zelada: None. K. Sabitha: None. J. Whitehair: None. A. Thomas: None. S. Samano: None. R. Voruganti: None. O. Lazarov: None. E.R. Bongarzone: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.13/Web Only

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

Support: Alzheimer's Society
New Frontiers in Research
CIHR

Title: Multimodal characterization of mouse models of TREM2, APOE, and humanized APP genes: Behavioural, metabolomic, and electrophysiological insights into sporadic Alzheimer's disease pathophysiology

Authors: ***B. MIRZA AGHA**¹, R. J. MCDONALD²;

¹Univ. of Lethbridge, Lethbridge, AB, Canada; ²Dept. of Neurosci., Univ. Lethbridge, Lethbridge, AB, Canada

Abstract: Sporadic Alzheimer's disease (SAD) is a multifactorial neurodegenerative disorder influenced by a combination of genetic and lifestyle risk factors. We characterized three transgenic mouse models relevant to SAD, carrying TREM2, APOE, and humanized APP genes at 3 and 9 months of age. TREM2 encodes a microglial receptor involved in immune signaling, APOE has a central role in lipid metabolism, and APP encodes the amyloid precursor protein whose cleavage generates amyloid-beta accumulation. These mice were evaluated across multiple domains including a battery of behavioural tasks targeting distinct memory systems, brain histology, blood serum metabolomic, and hippocampal electrophysiology. The results support our hypothesis that in the absence of lifestyle risk factor(s) or advanced aging, these genetic risk factors do not produce functional deficits. Given how little is known about SAD, this research provides a foundational framework for understanding its etiology and ultimately developing treatment options to prevent or slow its progression.

Disclosures: **B. Mirza Agha:** None. **R.J. McDonald:** None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.14/D1

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

Support: NIH/NIGMS R25GM130437
NIA K01 AG066747
NRSA (T32 GM148752)
AARG-21-846012
NIA 3P30 AG013319-25S1

Title: Plcg2 variants influence functional sex- and genotype specific differences in cognition, frailty, and brain lipids in a novel load mouse model

Authors: *J. GARCIA ROGERS¹, S. SMITH¹, S. FERNANDEZ¹, J. P. PALAVICINI², S. C. HOPP³;

¹Univ. of Texas Hlth. Sci. Ctr. San Antonio, San Antonio, TX; ²Univ. of Texas Hlth. Sci. Ctr. At San A, San Antonio, TX; ³Biggs Inst. for Alzheimer's and Neurodegenerative Dis., UT Hlth. San Antonio, San Antonio, TX

Abstract: PLCG2, the gene that codes for phospholipase C gamma 2 enzyme (plcg2), contains two polymorphisms associated with reduced (P522R) and increased (M28L) risk for Late-onset Alzheimer's Disease (LOAD). The P522R variant has been associated with increased longevity and functions as a hypermorph, whereas the M28L variant is thought to promote a slight loss of function of plcg2. The aim of these studies is to delineate behavioral, biochemical, and immunological phenotypes between PLCG2 variants in a novel LOAD mouse model (LOAD2) expressing humanized amyloid-beta, TREM2-R47H, and ApoE4. Three groups of LOAD2 mice, expressing wild type (WT), P522R, or M28L PLCG2 were used. At 12 months of age, mice underwent the Barnes Maze test. At 15 months, frailty analysis was conducted to evaluate differences in aging phenotypes between mice. At 19 months, frailty was reassessed. Mice were aged to 23 months then underwent brain harvesting for histological and biochemical analyses. The results from Barnes Maze indicated all mice learned how to escape the maze; however, M28L mice made significantly more errors during training and both M28L and P522R mice had significant deficits compared to controls during the memory-testing probe trial. Frailty testing revealed that in females only, M28L mice had higher scores than WT mice and P522R mice. When frailty was reassessed, there was an increase in the overall scores of all genotypes, with M28L still displaying the highest scores. Immunofluorescence staining revealed a trend towards a greater percentage of clasmatodendritic astrocytes in M28L mice compared to P522R mice within the hippocampus. Additionally, M28L mice indicated a reduction in percent area of GFAP compared to WT. Lipidomics analysis indicated that there are differences in myelin related lipids between PLCG2 genotypes and sex, with male P522R mice having a greater abundance of N-cerebrosides and N-sulfatides compared to their M28L and WT counterparts. In a different cohort of PLCG2 variant mice, frailty and spatial learning and memory was assessed at 12 months of age. Frailty analysis indicated elevated scores in C57BL/6J WTs, driven by female mice. Barnes Maze testing indicated learning deficits within P522R male mice, as well as reduced time spent in target quadrant during the re-probe trial. In summary, mice expressing M28L and P522R PLCG2 displayed slight deficits in learning and memory, sex-specific increases in frailty index scores, differences in clasmatodendritic astrocyte abundance, and myelin associated lipid abundance, suggesting these variants may play a functional role in altering various phenotypes relevant to aging and LOAD.

Disclosures: J. Garcia Rogers: None. S. Smith: None. S. Fernandez: None. J.P. Palavicini: None. S.C. Hopp: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.15/D2

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

Title: Mechanosensory Sleep Modulation as a Novel Therapeutic Strategy for Alzheimer's Disease in *Drosophila melanogaster*

Authors: ***R. GUERRIERO**;
George Mason Univ., Annandale, VA

Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder marked notably by cognitive decline, and accumulation of B-amyloid plaques and tau protein tangles. Current treatments are only symptomatic, highlighting the need for alternative therapeutic strategies. Recent studies suggest that sleep quality plays a role in modulating AD progression, with sleep disturbances commonly observed, even before cognitive symptoms. We investigated whether mechanosensory stimulation via rocking can promote sleep and alleviate cognitive decline in a *Drosophila melanogaster* model designed to express APP:BASE by manipulating the UAS-GAL4 system combined with GeneSwitch. Virgin female and male flies were monitored for sleep behavior using the *Drosophila* Activity Monitoring (DAM2) system, with sleep defined as periods of ≥ 5 minutes of inactivity. Mechanosensory stimulation through gentle rocking at 1.5 Hz was applied to promote sleep and assess its impact on sleep and short term memory. Initial results from the wild-type (w¹¹¹⁸) control flies showed increased sleep duration and longer sleep bouts during rocking, particularly during lights-off, indicating effective sleep induction. Moreover, rocking reduced overall sleep pressure, especially in virgin females, indicated by the decreased rebound sleep following stimulation. These findings support the hypothesis that rocking enhances sleep quality in flies. This process was repeated for another AD genetic model with flies expressing APP:BASE1 and MAPT, with also measuring short-term memory using aversive phototaxic suppression (APS) to assess learning and memory. This data was used to determine whether sleep enhancement via rocking can mitigate AD-related loss in short-term memory, and can be used as treatment or management of the disease in clinical populations. These findings provided preliminary evidence in *Drosophila*, that sleep induction through mechanosensory stimulation may serve as a non-pharmacological intervention to slow down AD progression. Future directions include analyzing amyloid and tau pathology and translating models to human clinical applications.

Disclosures: R. Guerriero: None.

Poster

PSTR011: Genetic Contributions to Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR011.16/D3

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

Title: Genetic rescue of lifespan and movement abilities in the Alzheimer's gene-expressing fruit fly (*Drosophila melanogaster*)

Authors: A. L. DRAPER¹, M. A. SPOONER¹, F. LIN², *R. M. YODER¹;

¹Psychology, ²Biol., Coastal Carolina Univ., Conway, SC

Abstract: The expression of Alzheimer's genes in fruit flies shortens their expected lifespan and alters their movements and climbing abilities in several behavioral tasks. However, we currently have limited evidence to indicate whether these deficits are reversible or otherwise treatable. Here, *Aβ42^{arc}*-expressing flies were generated by crossing an *Elav^{c155}Gal4* strain to a *UAS-Aβ42^{arc}* line (*Drosophila* Stock Center, Bloomington, IN). This *Elav-Gal4/UAS-Aβ42^{arc}* line (AD) was crossed to two control lines (UAS-luciferase RNAi and UAS-GFP). We then crossed the AD line to three different UAS-RNAi lines (cyclic nucleotide gated channel, lactate dehydrogenase, and serine protease) to evaluate the genetic rescue of lifespan and movement abilities. At ~21 days, flies were treated with CO₂ and then placed in a dark drawer for 30 mins. Flies were then placed individually in a 17 mm circular arena and an overhead camera recorded movement for 10 mins, once per week, across four weeks. Each fly's movements were later converted to x,y coordinates at 3 fps (Ethovision), and a movement analysis compared the organization and kinematic properties of flies' movements among Alzheimer's and rescue groups. All movements were sorted into short, medium, and long progressions, and total distance, peak speed, path circuitry, number of progressions, number of stops, and duration of stops were analyzed separately with custom analysis software (Excel). All three rescue groups' lifespans were significantly greater than the AD flies. During the first week of recording, the rescue groups showed significantly greater peak speeds, total distance, and number of long-, medium-, and short-length progressions than the AD group, with the serine protease group showing the greatest improvement. The serine protease group also showed the shortest average and total stop times, as well as the fewest stops. Our on-going analysis will determine whether this pattern of movement persists across the flies' lifespan. Overall, these results suggest that the genetic rescue procedures are able to partially restore lifespan and movement in flies that have a genetic predisposition for movement deficits.

Disclosures: A.L. Draper: None. M.A. Spooner: None. F. Lin: None. R.M. Yoder: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.01/D4

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

Title: Decoding neuroimmunity with spatial multiomics in a mouse model of Alzheimer's disease

Authors: J. BALLESTEROS¹, M. BONNET¹, C. SAYGILI DEMIR¹, S. AUBERT¹, P. MACHADO ALMEIDA¹, D. WAKHLOO², A. DIKSHIT³, M. PROCOPIO¹, *S. BRAJKOVIC¹;

¹Lunaphore Technologies, Tolochenaz, Switzerland; ²Bio-Techne, Newark, CA; ³Advanced Cell Diagnostics, Newark, CA

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder defined by the accumulation of amyloid-beta (A β) plaques, neurofibrillary tangles, synaptic dysfunction, and neuronal loss, ultimately leading to cognitive decline (PMID: 33986301). Despite significant advances in our understanding of AD, detailed mapping and characterization of the complex interplay between A β deposits and neuroinflammation in AD pathogenesis remains challenging. This study integrates multiplexed immunofluorescence and RNA in situ hybridization to map the cellular and molecular interplay between neurodegeneration and the neuroimmune landscape in a mouse model of AD.

Formalin-fixed paraffin-embedded coronal brain sections of an APP-PS1 transgenic mouse (PMID: 19936202) were stained and imaged on the fully automated COMETTM platform, combining RNAscopeTM (PMID: 22166544) HiPlex Pro and sequential immunofluorescence (seqIFTM, PMID: 37813886) protocols to enable simultaneous detection of up to 12-plex RNA and 24-plex protein targets on the same section. Image analysis, including spatial mapping of cell-type populations and quantitative assessment of protein and transcript expression at the single-cell level was done using the HORIZONTM software.

Multiplex protein marker panels enabled precise mapping of A β protein aggregates, neighboring cell populations, and their interactions in situ. Complementary RNA marker panels targeted genes involved in neuroinflammation responses and neuronal signaling. Integration of protein and RNA targets into the newly developed multiomics assay enabled comprehensive profiling of cell-specific responses around A β plaques, revealing coordinated alterations in immune activation and neuronal function. Spatial tissue analysis further identified local recruitment of reactive astrocytes and microglia to areas containing extracellular A β plaques. These glial cells exhibited a signature consistent with a pro-inflammatory phenotype, underscoring their role in AD pathophysiology.

This fully automated multiomics approach enables high-resolution spatial profiling of the cellular environment surrounding neurodegenerative lesions, providing new opportunities to explore the complex spatial and molecular interactions at the interface between neurodegeneration and neuroimmunity.

Disclosures: J. Ballesteros: A. Employment/Salary (full or part-time): Lunaphore Technologies. M. Bonnet: A. Employment/Salary (full or part-time): Lunaphore Technologies. C. Saygili Demir: A. Employment/Salary (full or part-time): Lunaphore Technologies. S. Aubert: A. Employment/Salary (full or part-time): Lunaphore Technologies. P. Machado Almeida: A. Employment/Salary (full or part-time): Lunaphore Technologies. D. Wakhloo: A. Employment/Salary (full or part-time): Bio-Techne. A. Dikshit: A. Employment/Salary (full or part-time): Bio-Techne. M. Procopio: A. Employment/Salary (full or part-time): Lunaphore Technologies. S. Brajkovic: A. Employment/Salary (full or part-time): Lunaphore Technologies.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.02/D5

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

Support: NIH Grant R01 CA172546
NIH Grant U01 AG032969
NIH Grant P01 CA186866
NIH Grant R56 AG061869
NIH Grant R01 AG067598
NIH Grant R01 AG074004
NIH Grant R01 AG072599

Title: Mapping epichaperome-driven network dysfunctions in Alzheimer's disease using dysfunctional protein-protein interactome analysis

Authors: *A. RODINA¹, S. BAY³, F. HAUT⁴, T. ROYCHOWDHURY¹, E. K. ARGYROUS⁵, A. STANISZEWSKI⁶, S. SHARMA¹, S. CHAKRABARTY¹, C. DIGWAL¹, A. STANISAVLJEVIC⁸, A. LABUZA¹¹, M. J. ALLDRED⁹, P. PANCHAL¹, H. SASAGURI¹², T. C. SAIDO¹³, D. A. BENNETT¹⁴, P. E. FRASER¹⁵, H. ERDJUMENT-BROMAGE¹⁶, T. A. NEUBERT¹⁷, S. D. GINSBERG¹⁰, O. ARANCIO⁷, G. CHIOSIS²;

¹Mem. Sloan Kettering Cancer Ctr., New York, NY; ²Chem. Biol. and Med., Mem. Sloan Kettering Cancer Ctr., NEW YORK, NY; ³CHEMICAL BIOLOGY, Sloan-Kettering Inst., NEW YORK, NY; ⁴Columbia Univ., Englewood, NJ; ⁵Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, ⁶Taub Inst., ⁷taub Inst., Columbia Univ., New York, NY; ⁸Biopharmaceutical Sciences, Nathan Kline Inst., Ridgewood, NY; ¹⁰Ctr. for Dementia Res., ⁹Nathan Kline Inst., Orangeburg, NY; ¹¹Psychology, Nathan S Kline Inst., Nanuet, NY; ¹²Dementia Pathophysiology Collaboration Unit, RIKEN Ctr. For Brain Sci., Wako-Shi, Japan; ¹³RIKEN Brain Sci. Inst. - Wako, Wako, Japan; ¹⁴Rush Alzheimer's Dis. Ctr., Rush Univ. Med. Ctr., Chicago, IL; ¹⁵Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; ¹⁶NYU Grossman Sch. of Med., New York, NY; ¹⁷New York Univ. Sch. of Med., New York, NY

Abstract: Neurodegenerative diseases such as Alzheimer's disease (AD) are increasingly recognized as disorders of progressive network failure, yet the molecular events that disrupt protein-protein interaction (PPI) networks during early disease stages remain poorly defined. In particular, the transition from normal cognition to mild cognitive impairment (MCI)—a critical inflection point in AD—remains molecularly elusive. To address this, we applied a chemoproteomic platform, dysfunctional Protein-Protein Interactome (dfPPI), to systematically map how PPI networks are rewired across the AD continuum. Using postmortem human brain samples spanning non-cognitively impaired (NCI), MCI, and AD patients, we leveraged epichaperomes—stable, stress-induced scaffolding assemblies of chaperones and co-chaperones—as disease-contextual capture probes for altered PPIs. Our analysis revealed

widespread and early network dysfunction, with 403 Reactome pathways dysregulated in MCI brains and 333 in AD. Strikingly, many disruptions were already present at the MCI stage, affecting key processes such as synaptic function, plasticity, neuroinflammatory signaling, translation initiation, phospholipid metabolism, and aberrant cell cycle reentry—functions previously implicated in AD pathogenesis but now linked mechanistically to epichaperome-mediated network remodeling. These findings offer a systems-level map of evolving protein network dysfunctions in AD and identify epichaperomes as upstream regulators of critical neuronal and glial pathways. By pinpointing when and how functional networks fail, this study highlights new opportunities to intervene before irreversible degeneration sets in—shifting the focus from late-stage pathology to early-stage prevention and network repair.

Disclosures: A. Rodina: None. S. Bay: None. F. Haut: None. T. Roychowdhury: None. E.K. Argyrousi: None. A. Staniszewski: None. S. Sharma: None. S. Chakrabarty: None. C. Digwal: None. A. Stanisavljevic: None. A. Labuza: None. M.J. Alldred: None. P. Panchal: None. H. Sasaguri: None. T.C. Saido: None. D.A. Bennett: None. P.E. Fraser: None. H. Erdjument-Bromage: None. T.A. Neubert: None. S.D. Ginsberg: None. O. Arancio: None. G. Chiosis: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.03/D6

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

Support: NIH/NIA AG079838

Title: Separation and isolation of selectively vulnerable and resilient neurons in culture

Authors: *M. YOKOMIZO¹, M. SADEK², E. WILLIAMS¹, V. DEROSLA¹, M. MAESAKO^{1,2};

¹Massachusetts Gen. Hosp., Boston, MA; ²Harvard Med. Sch., Boston, MA

Abstract: Neurodegenerative diseases, including Alzheimer's disease (AD), are characterized by progressive neuronal loss. Although individual neurons are genetically identical, they display distinct levels of susceptibility to toxicity. However, the causes and consequences underlying this cell-by-cell heterogeneity in neuronal vulnerability and resilience remain unclear. We recently developed a time-lapse live-cell imaging assay using propidium iodide (PI), allowing us to detect 1) which neuron dies in response to toxic insults, and 2) the time at which they die. This quantitative imaging platform has enabled us to capture the significant variability in response to oxidative stress caused by 4,4'-dithiodipyridine (DTDP) at the single cell resolution (Yokomizo *et al.*, 2024 in revision). We have now expanded this system by incorporating a sequential staining method using two different cell-impermeable dyes: SYTOX™ Green and PI. This new method has allowed us to reliably distinguish three categories of neurons, represented by

different colors: i) neurons dead at baseline—Yellow, ii) neurons that die in response to oxidative stress, i.e., vulnerable neurons—Red, and iii) neurons that survive even in the presence of the insult, i.e., resilient neurons—persistently fluorescence-negative. Furthermore, we have validated that fluorescence-activated cell sorting (FACS) with our sequential dual-dye staining approach can successfully separate and isolate the three neuronal subpopulations. We are currently conducting lipidomic analysis of membrane fractions from sorted vulnerable and resilient neurons to determine whether specific alterations in lipid profiles are associated with neuronal vulnerability and resilience. Our studies will enhance our understanding of the lipid membrane signatures of vulnerable and resilient neurons, which could potentially lead to the identification of novel therapeutic targets to enhance neuronal survival and diagnostic markers for neurodegenerative diseases.

Disclosures: M. Yokomizo: None. M. Sadek: None. E. Williams: None. V. Derosla: None. M. Maesako: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.04/D7

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

Title: Spatial proteomic mapping in Alzheimer's disease using multiplex immunostaining and AI-powered image analysis

Authors: A. KARPATI¹, V. AGRAWAL², E. LOCHE¹, S. STRUBLE², W. HOWAT¹, R. HEIL-CHAPDELAINE², N. FERNANDEZ DIAZ GRANADOS², *A. BOSE²;

¹Abcam Inc., Cambridge, United Kingdom; ²Leica Microsystems, Waltham, MA

Abstract: Alzheimer's disease (AD) is characterized by regionally selective neurodegeneration and complex proteinopathies, yet the spatial context of these molecular alterations remains poorly understood. To achieve a comprehensive spatial understanding of protein alterations across the AD brain, we employed Cell DIVE™, a high-plex, immunofluorescence-based imaging platform, for whole-brain multiplex spatial proteomic profiling combined with AI-based image analysis. Brain sections from AD patients and controls were stained using a novel panel of conjugated recombinant rabbit monoclonal (RabMAb®) antibodies from Abcam. Targets included markers of neurons, astrocytes, microglia, synapses, vascular structures, and AD pathology (amyloid-beta and phospho-tau). Cell DIVE enabled iterative rounds of staining, imaging, and fluorophore inactivation while maintaining tissue integrity. Advanced image analysis was performed using Aivia, an AI-powered software platform for segmentation, cell classification, and spatial analysis. This allowed precise mapping of protein expression at single-cell resolution and identification of spatially organized molecular networks. Our results revealed distinct, region-specific proteomic alterations, including differential expressions of synaptic proteins, compartmentalized glial activation, and co-localized neuronal cell populations

surrounding amyloid plaques and tau aggregates. Tau pathology showed progressive spatial gradients, correlating with altered neuronal and astrocytic protein profiles. This study demonstrates the power of combining multiplex immunostaining with AI-guided analysis to create a whole-brain spatial proteomic atlas of Alzheimer's disease. The integration of Cell DIVE, Aivia, and Abcam's directly conjugated recombinant antibodies enables scalable, reproducible, and high-resolution mapping of disease-relevant protein landscapes, providing valuable insight into the molecular architecture of neurodegeneration. Our findings provide new insight into region-specific molecular pathology and microenvironmental interactions, with implications for biomarker discovery and therapeutic targeting.

Disclosures: **A. Karpati:** A. Employment/Salary (full or part-time): Abcam Inc. **V. Agrawal:** A. Employment/Salary (full or part-time): Leica Microsystems. **E. Loche:** A. Employment/Salary (full or part-time): Abcam Inc. **S. Struble:** A. Employment/Salary (full or part-time): Leica Microsystems. **W. Howat:** A. Employment/Salary (full or part-time): Abcam Inc. **R. Heil-Chapdelaine:** A. Employment/Salary (full or part-time): Leica Microsystems. **N. Fernandez Diaz Granados:** A. Employment/Salary (full or part-time): Leica Microsystems. **A. Bose:** A. Employment/Salary (full or part-time): Leica Microsystems.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.05/D8

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

Support: NIH Duke-UNC Alzheimer's Disease Research Center P30AG072958

Title: The hippocampal proteomic response to military blast exposure exhibits significant overlaps in proteomic comparisons with synapse-related proteins altered in epilepsy and Alzheimer's disease datasets

Authors: B. EASTERLING¹, P. CAPTAN³, K. ADAMS², M. F. ALMEIDA⁵, ***B. A. BAHR**⁴;
¹Univ. of North Carolina at Pembroke, PEMBROKE, NC; ²Univ. of North Carolina at Pembroke, Pembroke, NC; ³Univ. of North Carolina, Pembroke, PEMBROKE, NC; ⁴Univ. of North Carolina, Pembroke, Pembroke, NC; ⁵McAllister Heart Institution, Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Blast waves have been linked to neurological issues including seizure susceptibility, and they account for thousands of veterans living with brain injuries. TBI has been associated with increased risks of Alzheimer's disease (AD) and a study of >350,000 veterans found mild TBI associated with 2.3 to 3.05-fold increases in dementia risk (Barnes et al. JAMA Neurol 2018 75:1055). Using a protocol developed with rat hippocampal explants, we previously found low-level military blasts to affect vulnerable components of brain circuitries before overt cellular damage (Smith et al. 2016 Exp Neurol 286:107; Almeida et al. 2021 Brain Pathology

31:e12936), reporting that detonations of RDX explosives (1.7-g assemblies) cause AD-related declines in synaptic markers and responses in correspondence with pathogenic tau staining. Here, the proteomic profile was determined 48 h after military blast exposure using label-free quantitative proteomics compared to adjacent hippocampal explants identically maintained after spending equal time in the blast chamber. Proteomics software statistically compared blast (n=4 groups of 7-8 explants each) vs. control samples (n=4). Comparisons were made with the proteomic signatures thoroughly described by the groups of Wisniewski and Drummond that found 89% of proteins altered in the hippocampus of epilepsy patients were also significantly altered in AD brains (Leitner et al. 2024 *Acta Neuropathologica* 147:27). They identified 105 synapse-related proteins altered in the same direction in epilepsy and AD, 88 of which were markedly decreased to suggest a common disease mechanism. Of these 88 proteins, 51% were significantly reduced in the blast profile. We also assessed the interactome network of 69 synaptic proteins identified by Leitner et al. and, interestingly, 96.7% of those detected in our dataset were reduced by blasts. Next, we compiled the blast effects for eight causative gene products for human epilepsy that were decreased in both epilepsy and AD. Among the six synaptic proteins, DNM1, SCN2A, STXBP1, SYNGAP1, and SYNJ1 were reduced 38-67% by blasts ($p=0.006-0.037$), while PURA was reduced insignificantly (-15%; $p=0.17$). For the two non-synaptic proteins, blast reduced SCLC25A22 60% ($p<0.01$) and GNAO1 by an insignificant 17%. The causative synaptic gene product SCN8a was reduced in epilepsy but increased in AD and was found reduced 63% by blast ($p=0.001$). Two causative factors increased in epilepsy, GABRA1 and EEF1A2, were reduced 53-58% by blasts ($p<0.01$) as were other GABA-A receptor subunits. The results point to synaptic alterations as important common links between blast-induced brain vulnerability, epilepsy, and AD.

Disclosures: B. Easterling: None. P. Captan: None. K. Adams: None. M.F. Almeida: None. B.A. Bahr: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.06/D9

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

Support: NIH Grant R56-AG049870
NIH Grant R01-AG059028
NIH Grant P30-AG066514
NIH Grant R01-AG078755
NIH Grant T32-AG049688

Title: Cortical layer-specific density changes of interneuron subtypes in Alzheimer's disease progression

Authors: *I. PAINE¹, L. LOWERY², E. MCDONOUGH², D. MEYER², J. I. LUEBKE³, P. R. HOF¹, M. VARGHESE⁴;

¹Icahn Sch. of Med. at Mount Sinai, New York, NY; ²GE HealthCare Technol. & Innovation Ctr., Niskayuna, NY; ³Anat. & Neurobio., Boston Univ., Boston, MA; ⁴George & Anne Ryan Inst. for Neurosci., Univ. of Rhode Island, Kingston, RI

Abstract: Neurodegeneration and the development of extracellular amyloid-beta plaques and intracellular neurofibrillary tau tangles show regional and cortical layer specificity in the progression of Alzheimer's disease (AD); however, the involvement of distinct cell types, characterized by protein expression, is insufficiently understood. We used multiplexed immunofluorescence to visualize interneuron subpopulations in postmortem tissue. We compared the dorsolateral prefrontal cortex (DLPFC), a region vulnerable to degeneration, to the primary visual cortex (V1), a less affected region, in humans across clinical dementia rating (CDR), Thal group, Braak group, and APOE genotype. Using scikit-learn, Support Vector Machine models were trained to segment cells (DAPI+) and classify all neurons (HuD+), as well as neurons expressing parvalbumin (PV+), calbindin (CB+), and/or calretinin (CR+). Cell density was calculated for each interneuron type by brain region, cortical layer, and score, group, or genotype, and analyzed using one-way ANOVA with Tukey HSD. With CDR, overall neuron density showed no significant changes in either DLPFC or V1. CB+ neuron density did not display significant changes with CDR, except in layer 6 of V1, where density was higher in CDR 0.5 compared to CDR 0 ($p = 0.04$) and CDR 3 ($p = 0.02$). CR+ and PV+ neuron density did not change with CDR in either DLPFC or V1. In layer 2 of V1, pre-AD and AD Thal group CB+ ($p = 0.01$) and CR+ ($p = 0.001$) neuron densities were significantly lower than control. Overall neuron density showed no significant decreases between Braak control versus AD stages in most layers. However, there was an increasing trend between Braak groups for all interneuron subtypes in most layers, which reached significance in layers 5 ($p = 0.04$) and 6 ($p = 0.02$) of DLPFC for CR+ neurons and layer 2 of DLPFC ($p = 0.02$) and layer 5 of V1 ($p = 0.04$) for PV+ neurons. Finally, there was a significant decrease in neuron density in APOE3/4 compared to APOE3/3 in layer 3 of DLPFC ($p = 0.04$). These results suggest interneuron subtypes may respond differently to various aspects of AD progression. That overall neuron density did not show significant decreases was unexpected, and is likely related to small group size and thin tissue sections. In previous stereological studies, pyramidal neuron subpopulations expressing non-phosphorylated neurofilament protein (NPNFP) decline in the DLPFC but not V1; NPNFP+ neuron density is currently being evaluated for these cases. These findings contribute to a larger understanding of selectively vulnerable neocortical neuronal populations in AD and overall progression of the disease in identified neuron types.

Disclosures: I. Paine: None. L. Lowery: None. E. McDonough: None. D. Meyer: None. J.I. Luebke: None. P.R. Hof: None. M. Varghese: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.07/D10

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

Support: NIH Grant R01AG075955

Title: Proteomics and transcriptomics of astrocytes and neurons in dementia-related contexts

Authors: ***M. ALONSO GARDON**¹, V. PANDEY², C. NEUPANE³, R. KAWAGUCHI¹, J. WOHLSCHEGEL¹, B. S. KHAKH⁴;

¹UCLA, Los Angeles, CA; ²Biol. Chem., UCLA, LOS ANGELES, CA; ³Dept. of Physiology, David Geffen Sch. of Med., Seoul Natl. Univ., Los Angeles, CA; ⁴Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Dementia is a common cause of cognitive decline and involves multiple contributing factors, including aging, amyloid beta (A β) plaques, and neuroinflammation. Aging is the strongest risk factor for dementia, though not its direct cause. In certain forms of dementia, the accumulation of A β plaques disrupts cellular homeostasis and neuronal communication, while neuroinflammation exacerbates neuronal dysfunction and glial reactivity. Together, these pathological features lead to widespread changes in brain cell populations and molecular alterations, particularly in astrocytes and neurons. Previous studies have primarily focused on gene expression analyses in these cell types. However, in the context of dementia, astrocytes and neurons have not been thoroughly examined together, and little is known about how their proteomes change across different conditions. We studied these changes by combining immunohistochemistry, electrophysiology, transcriptomics, and in vivo proximity-based proteomics. Astrocyte density increased in layers 2/3 of the motor cortex with age, while neuron, microglia, and oligodendrocyte numbers remained unchanged. Aging was also associated with reduced astrocyte morphology, suggesting astrocytes may be especially sensitive. Electrophysiological recordings showed reduced gap junction coupling and lower Ba²⁺-sensitive potassium conductance in aged astrocytes. In contrast, neurons displayed reduced dendritic spine density without changes in soma size or intrinsic properties. To assess molecular changes, we used BioID2-based biotinylation to label subproteomes in astrocytes and neurons across aging, A β pathology, and neuroinflammation. These data were compared to cell type-specific Rpl22-HA-based transcriptomic profiles. Structural changes were linked to alterations in key proteins related to astrocyte territory size. Comparative analysis also revealed both shared and cell type-specific proteomic changes. These involved altered pathways such as protein trafficking, lipid metabolism, ion and small molecule transport, synaptic transmission, and autophagy. Our findings provide critical insight into the molecular mechanisms driving dementia-related brain dysfunctions

Disclosures: **M. Alonso Gardon:** None. **V. Pandey:** None. **C. Neupane:** None. **R. Kawaguchi:** None. **J. Wohlschlegel:** None. **B.S. Khakh:** None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.08/D11

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

Support: NIA Grant RO1AG068293

Title: Single-neuron spatial proteomics reveals distinct signatures of healthy and pathological brain aging

Authors: *H. HUDSON^{1,2}, T. ORR^{1,2,3}, X. SUN^{1,2}, C. WILLIAMS⁴, H. SATO^{1,2,3}, M. ORR^{1,2,3,5};

¹Neurol., Washington Univ. Sch. of Med., St. Louis, MO; ²Bruker Spatial Biol. Ctr. of Excellence, Washington Univ. Sch. of Med., St. Louis, MO; ³Tracy Family SILQ Ctr., St. Louis, MO; ⁴Bruker Spatial Biol., Seattle, WA; ⁵St. Louis VA Med. Ctr., St. Louis, MO

Abstract: Neurons with tau-containing neurofibrillary tangles (NFTs) are closely associated with Alzheimer's disease (AD) progression and severity. Our previous work demonstrated that NFT-bearing neurons undergo a cell fate change consistent with cellular senescence. Senescence is a complex stress response in which cells resist apoptosis and drive inflammation and tissue degeneration across their neighborhood. Here, we evaluated the expression of 86 proteins related to neuropathology, inflammation, autophagy, and cell identity in normal and NFT-bearing neurons across the human lifespan using non-destructive, multiplexed, spatially resolved profiling. We analyzed postmortem hippocampus (CA1) and entorhinal cortex from males and females spanning eight decades of life. Samples included 40 individuals aged 20-59 (10 per decade) and 120 individuals aged 60-99 (10 per Braak stage group [I-II, III-IV, V-VI] per decade). Regions of interest, each containing a single neuron, were selected based on neuronal AT8 immunoreactivity (phosphorylated tau at Ser²⁰²/Thr²⁰⁵), identifying NFTs, and profiled using the GeoMx® Digital Spatial Profiling platform. The dataset includes over 18,000 single neurons. NFT-bearing neurons were compared to neighboring healthy neurons within and across individuals. These analyses validated and extended prior observations of a senescent-like phenotype in NFT-positive neurons. Proteomic patterns were also evaluated across aging. Several proteins, including non-pathogenic forms of tau and amyloid, showed non-linear trajectories across the lifespan resembling those found in peripheral blood proteomics, suggesting conserved aging processes across tissues. In contrast, pathogenic forms of tau and amyloid diverged from these systemic patterns, potentially reflecting neuron-specific disease mechanisms. This study provides molecular insight into the distinction between healthy and pathological brain aging and identifies senescent-like neurons as a potential target for therapeutic intervention in AD.

Disclosures: H. Hudson: None. T. Orr: None. X. Sun: None. C. Williams: A.

Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. H. Sato: None. M. Orr: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.09/D12

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

Support: NIH 130862
25AARF-1376894

Title: Chronic Stress Alters Gene Expression Across Brain Cell Types with Enrichment for Neurodegenerative Signatures

Authors: *C. MARTIN¹, S. YAN², A. BOMBIN¹, K. JIAO³, Q. WANG⁴;
¹Augusta Univ., augusta, GA; ²Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA;
³Med. Col. of Georgia at Augusta Univ., Augusta, GA; ⁴Neurosci. and Regenerative Med., Med. Col. of Georgia, AUGUSTA, GA

Abstract: Chronic stress is a significant risk factor for depression and dementia, including Alzheimer's disease (AD). However, the genetic and epigenetic mechanisms underlying stress-induced brain dysfunction remain incompletely understood. The chronic unpredictable mild stress (CUMS) model simulates the daily stressors experienced in human life, showcasing behavioral and neurobiological changes similar to those observed in depression disorders. We employed single-nucleus multiome sequencing to simultaneously profile transcriptomic and epigenomic changes in the hippocampus of mice subjected to 6-week CUMS. This approach revealed widespread alterations in transcriptomics and chromatin accessibility across diverse hippocampal cell types. Significantly, we observed that CUMS led to significant dysregulations in gene sets associated with multiple neurodegenerative disorders, including Alzheimer's disease. . This result aligns well with clinical observations that chronic stress predisposes individuals to neurodegenerative diseases, providing potential molecular connections between stress and these neurological conditions. Furthermore, Oligodendrocytes exhibit heightened vulnerability, with CUMS disrupting oligodendrocyte precursor cell (OPC) differentiation, migration, and intercellular communication, leading to myelination deficits. Given the growing recognition of OPC/ODC involvement in AD pathogenesis, their vulnerability to chronic stress may represent a converging mechanism linking prolonged psychological stress to increased AD risk, highlighting the importance of preserving oligodendroglial health in both stress-related and neurodegenerative contexts.

Disclosures: C. Martin: None. S. Yan: None. A. Bombin: None. K. Jiao: None. Q. Wang: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.10/D13

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

Support: Chan Zuckerberg Initiative (2019-199150)

Title: Resolving glial heterogeneity through integrative topic modeling, and spatial transcriptomics in Alzheimer's disease

Authors: *A. SANKARAESWARAN¹, J. PAN², J. SANZ-ROS³, I. COBOS⁴;

¹Stanford Univ., Fremont, CA; ²Pathology, Stanford Univ., Palo alto, CA; ³Dept. of Pathology, Stanford Univ. Sch. of Med., Mountain View, CA; ⁴STANFORD UNIVERSITY, Stanford, CA

Abstract: Glial cells exhibit a dynamic continuum of transcriptional states that shift in response to microenvironmental cues during disease progression. Although single-nucleus and spatial transcriptomic technologies have improved resolution, accurately delineating glial subtypes remains difficult due to high transcriptional overlap, subtle expression gradients, and non-discrete state transitions that challenge conventional clustering algorithms. We developed an integrative framework that combines graph-based clustering and topic modeling to resolve glial heterogeneity at high resolution. Our dataset included over 100,000 nuclei from the human prefrontal cortex across 16 donors, including control and Alzheimer's disease cases. Leiden clustering was applied in PCA space across multiple resolutions to capture both broad and fine-grained glial subpopulations. Cluster-level expression profiles were computed by averaging gene expression within each group. To uncover latent gene expression programs, we applied non-negative matrix factorization (NMF) using FaStaNMF across 4-15 topics. The optimal model was selected using multiple criteria, including topic stability, coherence scores (via Gensim), BIC, AIC, and reconstruction error. Final topic models revealed continuous gene programs, which we aligned with discrete clusters by selecting the Leiden resolution that best matched topic-based marker profiles. To assess spatial relevance, we performed Xenium spatial transcriptomics in the same region using a 366-gene targeted panel (human Neuroscience panel and 100-gene custom add-on). This revealed distinct spatial distributions of glial states, including region-specific astrocyte and oligodendroglia programs. Our framework bridges discrete and continuous models of cell identity and enables robust spatial mapping of glial diversity in the human brain.

Disclosures: A. Sankaraeswaran: None. J. Pan: None. J. Sanz-Ros: None. I. Cobos: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.11/D14

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

Support: Cure Alzheimer's Fund

Title: The diversity of disease-associated natural human antibodies and antibodies targeting amyloid beta sheet structure decline dramatically in Alzheimer's disease.

Authors: *J. M. REYES-RUIZ¹, J. ZHANG², Z. YU³, C. G. GLABE⁴;

¹Mol. Biol. and Biochem., Univ. of California, Irvine, Irvine, CA; ²University of California, Irvine, Irvine, CA; ³University of California Irvine, Irvine, CA; ⁴Mol. Biol. and Biochem., Univ. California, Irvine, Irvine, CA

Abstract: Monoclonal antibodies targeting Ab amyloid have been approved as therapeutic agents for AD, but little is known about natural human antibodies (NAbs) associated with AD and some is contradictory. We have developed "Epitomic Profiling" (EP) as an unbiased tool for identifying the set of peptide epitope segments (ES) for antibodies in human serum and quantifying them. EP involves the immunoselection of random 12-mer amino acid sequences from a phage display library followed by deep sequencing and allows the quantitation of the level of thousands of individual NAbs in blood. The sequences are tiled in 9 overlapping tetramers representing ES and non-specific tetramers filtered out. Tetramers are the optimum combination of specificity and sensitivity for finding an initial ES and larger more unique epitopes are subsequently built by combining overlapping and correlated discontinuous ES. The NAb-specific ES are then compared in the AD and age matched cognitively normal (NC) populations by multiple Mann-Whitney U test to find differentially expressed epitope segments (DEES). We found that disease associated DEES are dramatically reduced in AD. While 310 tetrameric DEES are elevated in AD, 11,079 are elevated in NC after FDR correction ($q < 0.05$), indicating that the diversity of NAbs declines dramatically in AD. Many of these DEES map to amyloids that accumulate in AD, such as Ab42, tau, α -synuclein, TDP43 and TMEM106b. NAbs binding to Ab are elevated in both the AD and NC populations with those elevated in AD mapping to residues 1-7 and 17-20 of the Ab sequence. This specificity includes many of the antibodies used in human clinical trials. NAbs binding to residues 7-12 and the carboxyl terminal region are elevated in NC. Amyloid b-sheets contain low complexity epitopes formed by linear tracts of amino acid side chain "spines" on the parallel, in-register structure of the fibril where the sequence of each strand is identical to the ones above and below in the sheet. To search specifically for NAbs that may bind to these quasi-crystalline side chain tracts that alternate in sequence on opposite sides of the sheet, we tiled the sequence in alternating wild card b-sheet heptamers (1x3x5x7) where x can be any amino acid. We found that 14,578 wild card b-sheet heptamers are elevated in the NC population while only 675 are elevated in AD, suggesting that some of the dramatic decline in antibody diversity may be due to the absence of protective antibodies that bind to low complexity epitopes on the amyloid b-sheet surface. Supported by the Cure Alzheimer's fund.

Disclosures: J.M. Reyes-Ruiz: None. J. Zhang: None. Z. Yu: None. C.G. Glabe: F. Consulting Fees (e.g., advisory boards); AltPep corporation.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.13/D16

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

Title: Spatial Multiomic Profiling of Human Frontal Cortex Reveals Molecular and Cellular Mechanisms of Alzheimer's Disease at Single-Cell Subcellular Resolution

Authors: N. JOSHI¹, M. PATRICK², Q. HUANG¹, W. YANG², R. ROOZAFZON¹, M. XIMERAKIS¹, M. RHODES², A. HECK², J. LYSSAND², P. DIVAKAR², A. TAMBURINO¹, *S. HE², J. BEECHEM², V. PETERSON¹;
¹Merck & Co., Inc, Cambridge, MA; ²Bruker Spatial Biol., Seattle, WA

Abstract: Comprehensive understanding of Alzheimer's disease (AD) requires spatially resolved, single-cell characterization of both gene and protein expression within the complex architecture of the human brain. We employed the CosMx® Spatial Molecular Imager (SMI) to perform spatial multiomic analysis on formalin-fixed paraffin-embedded (FFPE) human parietal cortex tissue from cognitively normal individuals and patients with Alzheimer's disease. Serial sections were analyzed using the CosMx® Whole Transcriptome Assay (~19,000 genes) and the CosMx® 64-plex Neural Protein Assay. We demonstrate high technical performance of both assays, with robust detection of a broad range of transcripts and proteins across diverse cell types. The integration of protein data significantly enhanced cell type resolution beyond transcriptomic profiling alone, enabling confident identification of neuronal, glial, vascular, and immune cell populations, including subtle subtypes and activation states. Biological insights from the combined datasets revealed spatially distinct cellular responses associated with AD pathology. We observed reorganization of the cellular microenvironment surrounding amyloid plaques, including localized glial activation and altered neuronal composition. Spatial patterns of neuroinflammation and immune cell activation were evident. The data also revealed spatial gradients and niche-specific alterations in gene and protein expression, pointing to regionally patterned disease vulnerability. Finally, spatial gene correlation analysis using the InsituCor algorithm and spatial Reactionome pathway analysis reveals altered cell-cell communications and signaling dynamics in plaque-associated regions, suggesting disruption of normal intercellular interactions in Alzheimer's disease. Together, these results illustrate the power of spatial multiomics to characterize the molecular and cellular landscape of Alzheimer's disease in situ. By combining high-plex RNA and protein imaging, we demonstrate a technically robust and biologically informative approach for uncovering spatial mechanisms underlying neurodegeneration, indicating a strong potential for the discovery of novel biomarkers and therapeutic targets.

Disclosures: N. Joshi: None. M. Patrick: None. Q. Huang: None. W. Yang: None. R. Roozafzon: None. M. Ximerakis: None. M. Rhodes: None. A. Tamburino: None. S. He: None. J. Beechem: None. V. Peterson: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.14/D17

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

Support: NIH Grant 1R03AG092563

Title: Spaceflight impacts gene associated with neurodegenerative disorders in glial cells which may be ameliorated by exercise

Authors: D. PIEKARSKI, *M. W. MCNERNEY;
VA, Palo Alto, CA

Abstract: Exposure to stress impacts brain health and increases risk for neurodegenerative disease, including Alzheimer's Disease. This is a significant concern for astronauts, many of whom are military veterans, given that spaceflight rate and duration is increasing rapidly and space missions include significant psychological (confinement, isolation) and physiological (radiation exposure, microgravity) stressors. As such, it is necessary to understand how spaceflight impacts brain health and to develop tractable methods to mitigate those effects. One strong candidate method to ameliorate spaceflight includes aerobic exercise, which builds brain resilience to stress and reduces the onset/progression of neurodegenerative disease. We report results from an ongoing project that is analyzing public single nucleus RNAseq datasets in mice to understand how spaceflight impacts genes associated with Alzheimer's Disease and neurodegeneration and how aerobic exercise impacts these genes. By analyzing NASA's Open Sciences Data Repository experiment OSD-613, in which mice either visited the international space station for ~55 days or were maintained as ground controls, we have found that spaceflight induces significant gene expression changes to hundreds of genes in microglia, astrocytes, oligodendrocytes and oligodendrocyte precursor cells. Followup KEGG pathway analyses revealed enriched pathways for neurodegenerative diseases, including Alzheimer's Disease and Parkinson's Disease, oxidative stress, and cell death pathways including ferroptosis and apoptosis across each glial cell subtype. Many of these genes overlap with those found to be impacted by chronic aerobic exercise (GEPREP; Sun et al., 2025). Glial cells have recently been recognized as key contributors to the etiology and progression of neurodegenerative disease and these results strongly suggest that spaceflight is associated with glial cell stress and death, and likely enhance risk for neurodegeneration. These results will inform the unique post-service healthcare needs of astronauts, many of whom are veterans and will serve as an important model for military related, multivariate stressors, which often include overlapping psychological and physiological stressors.

Disclosures: D. Piekarski: None. M.W. McNerney: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.15/D18

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

Support: NIA Grant RO1AG068293

Title: Integrated Spatial Transcriptomic and Proteomic Profiling with Same-Slide Orthogonal Validation Reveals Distinct Plaque Microenvironments in Human Neurodegenerative Disease

Authors: O. BRAUBACH¹, *H. SATO^{6,7,8}, T. C. ORR^{9,7,8}, A. HECK², L. WU³, M. H. INGALLS⁴, A. NORTHCUTT⁵, C. D. KEENE¹¹, J. M. BEECHEM², M. E. ORR¹⁰;

¹Bruker Spatial Biol., St. Louis, MO; ³Res. and Develop., ²Bruker Spatial Biol., Seattle, WA;

⁴Bruker Spatial Biol., Saint Louis, MO; ⁵Bruker Spatial Biol., St Louis, MO; ⁶1-Washington Univ. Sch. of Medicine, Dept. of Neurology, St Louis, MO, USA; 2-Tracy Fam, St Louis, MO;

⁷Tracy Family SILQ Center, Washington Univ., St Louis, MO; ⁸Bruker Spatial Biol. Ctr. of Excellence, St Louis, MO; ⁹Neurol., ¹⁰Intrnl. Med., Washington Univ. Sch. of Med., St Louis, MO; ¹¹Pathology, Univ. of Washington, Seattle, WA

Abstract: Amyloid plaque deposition is a hallmark of Alzheimer's disease (AD), but also occurs in clinically normal older adults and other neurodegenerative diseases such as Parkinson's disease and ALS. Spatial transcriptomic studies have shown that molecular responses to amyloid pathology are highly context-dependent, shaped by disease stage, brain region, and cellular composition. However, transcriptomic data alone may not fully reflect protein-level changes due to limitations in detection sensitivity, translation efficiency, and protein stability. To address this, we developed a same-slide, multiplatform spatial profiling pipeline that enables orthogonal validation across transcriptomic and proteomic modalities. Using the GeoMx[®] Digital Spatial Profiler (DSP), we performed simultaneous whole-transcriptome and 643-plex protein profiling on FFPE human brain tissue. Regions of interest were centered on amyloid plaques in the primary motor and visual cortices from four diagnostic groups: non-demented controls, AD with neuritic plaques (NP), AD without NP, and ALS. NP are associated with hyperphosphorylated tau, reactive glial cells, synaptic dysfunction, lysosomal accumulation, and oxidative stress—features best captured through high-plex multiomic approaches. Following GeoMx profiling, we profiled the same slides using CellScape[™], a multiplex immunofluorescence platform with single-cell resolution and high dynamic range microscopy. This same-slide orthogonal approach preserved spatial integrity and enabled precise cross-platform validation. CellScape confirmed DSP-derived protein targets, resolved subcellular localization, and identified features underrepresented in transcriptomic data, such as extracellular proteins and acellular plaque-core components. This integrated pipeline revealed distinct molecular signatures in plaque microenvironments that varied by disease condition and brain region. Our findings demonstrate the value of combining high-plex spatial profiling with same-slide single-cell validation and provide a generalizable framework for multiomic analysis of complex human neuropathology.

Disclosures: O. Braubach: A. Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. H. Sato: None. T.C. Orr: None. A. Heck: A. Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. L. Wu: A. Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified

mutual funds); Bruker Spatial Biology. **M.H. Ingalls:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **A. Northcutt:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **C.D. Keene:** None. **J.M. Beechem:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bruker Spatial Biology. **M.E. Orr:** None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.16/D19

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

Support: R01NS111220
NIH-1R01NS111220-01

Title: Unraveling the Role of Cell Death Pathways in Alzheimer's Disease: Insights from Imaging Mass Cytometry Analysis in AD Mouse Models and Human Brain Tissues

Authors: ***J. SHI**¹, Y. SHI¹, W. LIU², A. SONG¹, T. SANNI¹, E. ZUNDER³, C. DEPPMANN¹; ¹Univ. of Virginia, Charlottesville, VA; ²Univ. of Virginia Neurosci. Program, Charlottesville, VA; ³Biomed. Engin., Univ. of Virginia, Charlottesville, VA

Abstract: Alzheimer's disease (AD) is characterized by extensive neuronal loss, yet how and when cell death happens remain unclear. While individual cell death pathways including apoptosis, necroptosis, and pyroptosis have been implicated in AD, their temporal progression and spatial distribution have not been comprehensively investigated. A better understanding of the mechanisms and timing of cell death may help delineate disease pathogenesis and provide insights toward treatment. We employed imaging mass cytometry (IMC) to simultaneously visualize over 40 metal-conjugated antibodies in brain tissues from four mouse models: 5xFAD, PS19, 5xFAD×PS19 double mutant, and controls (n=4 per group, both sexes, ages 3, 6.5, 9 and 12 months) and post-mortem human AD patients and age-matched controls (n=6 per group). We developed and validated a comprehensive antibody panel consisting of three main components: (1) cell identity markers targeting neurons, microglia, oligodendrocytes, astrocytes, and endothelial cells; (2) AD pathology markers (A β and Tau); and (3) DNA damage and cell death markers, including γ H2AX for DNA damage, cleaved caspase-3 for apoptosis, RIPK1 and phosphoMLKL for necroptosis, and ASC for pyroptosis. IMC staining was performed on 5 μ m FFPE sections with regions of interest in cortex and hippocampus. Images were processed using IMC-Denoise for hot pixel removal, Mesmer for cell segmentation, and clustering algorithms for cell type identification. Spatial analysis employed k-nearest

neighbor graphs and cellular neighborhood detection to quantify cell death marker distribution relative to AD pathology. Preliminary results revealed microglia exhibited significantly closer proximity to A β plaques compared to other cell types ($p < 0.01$). Age-dependent analysis demonstrated progressive accumulation of cell death markers in neuronal populations, with distinct temporal patterns across mouse models. These findings demonstrate that multiple cell death pathways contribute to neuronal loss in AD with distinct spatiotemporal patterns, providing mechanistic insights for targeted neuroprotective strategies.

Disclosures: J. Shi: None. Y. Shi: None. W. Liu: None. A. Song: None. T. Sanni: None. E. Zunder: None. C. Deppmann: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.17/D20

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

Support: STI2030-Major Projects (2022ZD0211600)
National Natural Science Foundation of China (82071201, 82271471, 92249305)
Shanghai Municipal Science and Technology Major Project (2023SHZDZX02)
Excellent Academic Research Leader Program of Shanghai (23XD1420400)
Emerging Interdisciplinary Research Project of Shanghai (2022JC014)
Research Start-up Fund of Huashan Hospital (2022QD002)
Excellence 2025 Talent Cultivation Program at Fudan University (3030277001)

Title: Divergent Cellular Program Progression with a Pallial Division in Alzheimer's Disease

Authors: Y.-N. HAO¹, *P. YUAN², J.-T. YU³;

¹Huashan Hospital, Fudan University, Shanghai, China; ²Fudan Univ., Shanghai, China; ³Huashan Hospital, Fudan Univ., Shanghai, China

Abstract: Amyloid plaques drive cellular abnormalities in Alzheimer's disease (AD). It is unclear, however, why different brain regions exhibit distinct pathological expressions. Here, we combined spatial transcriptomics with *in-situ* amyloid staining and single-nuclei sequencing in adjacent seven defined brain regions in 5xFAD mice. We curated a total of 12,360,215 spatially resolved transcriptomes and 1,758,342 single-nuclei data from 7 age groups, and developed a quantitative tool for spatially tuned transcriptional modules. Importantly, we discovered ontogenically distinct subpallial microglia subtypes that express neuropeptides with heightened reactivity to plaques, accompanied with selective apoptosis of cholinergic neurons in plaque-

microenvironment in this region. We verified these findings in postmortem AD patients' brains. Our study provides an unprecedented resource for dissecting brain region specific progression of plaque-associated pathogenesis, now accessible online.

Disclosures: Y. Hao: None. P. Yuan: None. J. Yu: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.18/D21

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

Support: the Research Grants Council of Hong Kong (the Collaborative Research Fund [C6027-19GF], the Theme-Based Research Scheme [T13-605/18W], and the General Research Fund [HKUST16103122, HKUST16102824, and HKUST16104624])
the Areas of Excellence Scheme of the University Grants Committee (AoE/M-604/16)
the InnoHK initiative and grant [ITCPD/17-9] of the Innovation and Technology Commission of the HKSAR Government
SIAT-HKUST Joint Laboratory for Brain Science (Joint Laboratory Funding Scheme [JLFS/M-604/24])
the Guangdong-Hong Kong Joint Laboratory for Psychiatric Disorders (2023B1212120004)

Title: Spatial transcriptomic investigation of the molecular alterations in brain cells in association with amyloid plaque deposition in Alzheimer's disease

Authors: *X. YANG^{1,2}, X. WANG¹, Y. QIAO¹, W. WU^{1,2}, W.-Y. FU^{1,2}, A.-Y. FU^{1,2,3}, N. Y. IP^{1,2,3},

¹Div. of Life Science, State Key Lab. of Nervous Syst. Disorders and Daniel and Mayce Yu Mol. Neurosci. Center, The Hong Kong Univ. of Sci. and Technol., Hong Kong Special Administrative Region, China; ²InnoHK, Hong Kong Ctr. for Neurodegenerative Dis., Hong Kong Special Administrative Region, China; ³Guangdong Provincial Key Lab. of Brain Science, Dis. and Drug Development, HKUST Shenzhen Res. Institute, Shenzhen-Hong Kong Inst. of Brain Sci., Shenzhen, Guangdong, 518057, China

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no effective cure, characterized by the extracellular deposition of amyloid plaques. Microglia sense these amyloid plaques and undergo cellular and functional changes that enable them to migrate towards and clear the plaques. Surface receptors on microglia (e.g., VCAM1 and TREM2) are crucial for mediating the transition from a homeostatic to a chemotactic state, leading to a disease-associated state. However, the underlying mechanisms of how these surface receptors

mediate state transitions in response to amyloid plaque depositions remain unclear. To address this, we investigated the spatial relationships between various microglial subtypes and amyloid plaques, along with their associated molecular changes. Identifying different surface receptors on microglial subtypes may enhance our understanding of their regulatory mechanisms.

Accordingly, we studied the molecular changes in microglia located at varying distances from amyloid plaques in transgenic AD mouse models, using spatial transcriptomics and single-nucleus/single-cell transcriptome analysis in APP/PS1 transgenic AD mice. We aligned the immunostained amyloid plaque signals with the spatial transcriptomic data on the same mouse brain sections, and conducted the transcriptomic analysis in plaque-associated and non-plaque-associated microglia in the cortex and hippocampus of APP/PS1 mice. We then characterized the microglial subtypes at varying distances from the amyloid plaques and analysed the differentially expressed genes and pathway alterations in microglia. We identified candidate surface receptors that are prominently expressed in plaque-associated microglia. By co-analyzing expression of these receptors with microglial state markers, we uncovered the potential biological pathways in these amyloid-associated microglia. Together, our findings suggest molecular mechanisms that drive microglial state changes in amyloid clearance.

Disclosures: X. Yang: None. X. wang: None. Y. Qiao: None. W. Wu: None. W. Fu: None. A. Fu: None. N.Y. Ip: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.19/D22

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

Title: Chimeric antibodies in Alzheimer research: properties and application in low-multiplexing assays

Authors: T. BRIGHT¹, A. KARPAT², T. BARNES¹, A. GALLI¹, *W. HOWAT³, S. SBACCHI¹;

¹Abcam Ltd, Cambridge, United Kingdom; ²Abcam Inc., Cambridge, United Kingdom; ³Abcam, Cambridge, United Kingdom

Abstract: Chimeric antibodies, engineered by fusing the variable (antigen-binding) domains of one species (e.g. rabbit) with the constant domains of a different species (e.g. human, chicken), represent a significant advancement in antibody technology. This design allows the development of antibodies that retain the original antibody's specificity and affinity, while also incorporating desirable features from the new species. Beyond therapeutics, the distinctive characteristics of chimeric antibodies offer notable benefits in *in vitro* diagnostic and research applications, for example in low-multiplexing assays. In particular, chimeric antibodies offer significant advantages in multiplexed assays, where their species-specific constant regions allow for the simultaneous use of multiple primary antibodies with minimal cross-reactivity. The use of

chimeric antibodies is compatible with diverse experimental setups allowing researchers to leverage existing secondary antibodies systems. Here we show the advantage of using chimeric antibodies for building immunohistochemistry (IHC) panels for the co-detection of common neuronal and glial cell markers and Alzheimer's disease (AD) protein markers in formalin-fixed paraffin-embedded (FFPE) human brain normal and AD tissues. By leveraging antibodies derived from multiple host species, including mouse, rabbit, and chicken, we achieved robust and specific staining in both normal and AD brain samples. Our results highlight the potential of chimeric antibodies to streamline complex IHC workflows and improve the resolution of multiplexed tissue analyses in neurodegenerative disease research.

Disclosures: **T. Bright:** A. Employment/Salary (full or part-time): Abcam. **A. Karpati:** A. Employment/Salary (full or part-time): Abcam. **T. Barnes:** A. Employment/Salary (full or part-time): Abcam. **A. Galli:** A. Employment/Salary (full or part-time): Abcam. **W. Howat:** A. Employment/Salary (full or part-time): Abcam. **S. Sbacchi:** A. Employment/Salary (full or part-time): Abcam.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.20/D23

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

Support: NIA U01 AG088683
NIA U54 AG054345
NIA R56 AG083940

Title: Synergistic effects of toxic metals and Alzheimer's genetics on brain aging in novel humanized mouse model LOAD3e4

Authors: ***Z. SARICA**¹, K. P. KOTREDES¹, O. MINAEVA², J. A. MONCASTER², S. PERSOHN³, L. CEOTTO FREITAS LIMA³, A. PODDER¹, D. AYLOR⁴, G. W. CARTER¹, P. R. TERRITO³, L. E. GOLDSTEIN², G. R. HOWELL¹;

¹The Jackson Lab., Bar Harbor, ME; ²Mol. Aging and Develop. Lab., Boston Univ., Boston, MA; ³Stark Neurosci., Indiana Univ., Indianapolis, IN; ⁴North Carolina State Univ., Raleigh, NC

Abstract: Late-onset Alzheimer's disease (LOAD), accounting for over 90% of all AD cases, remains a complex challenge in neurodegenerative research. While individual contributions of aging, genetics and environmental exposures to LOAD are well-studied, their synergistic interactions have received comparatively little attention. To address this, we established the TOX-AD Center to investigate how environmental toxicant exposures interact with AD genetics to affect the pathobiology of AD. Our research leverages novel mouse models that express humanized AD risk genes. In this gene-environment interaction study, we hypothesize that toxic

metal exposure disrupts cerebrovascular integrity, promotes neuroinflammation and induces brain biometal dyshomeostasis. Novel MODEL-AD mouse models were exposed to three common neurotoxic metals during two neurodevelopmental windows: prenatal to early adult and early adult to aged. Exposure via drinking water ad lib at human-relevant doses of arsenic, cadmium, and lead. Post-exposure, all mice will have gone a comprehensive in vivo phenotyping, including behavior, cognition and neuroimaging (PET/CT) to assess humanized amyloid-beta (hA β) deposition, regional brain perfusion, and blood-brain barrier integrity. Brains were hemisected for downstream analyses including metallomic imaging mass spectrometry, immunohistochemistry, and multi-omics profiling. Blood samples were collected for biomarker discovery and epigenomic profiling. We generated B6J.hAPOE4.hAbeta.hMAPT-GR (LOAD3e4) and B6J.hAPOE3.hAbeta.hMAPT-GR (LOAD3e3) mouse strains through the MODEL-AD Center. Our preliminary findings using B6J.hAPOE4.hAbeta mice showed evidence that these neurotoxicants accumulate in the brain and alter the expression of LOAD-relevant genes. In a pilot study with LOAD3e4, B6 controls did not express plasma hA β 40 or hA β 42, while metal exposure increased these levels in LOAD3e4 mice, supporting the AD-like relevance of our paradigm. These levels also varied depending on the specific metal treatment, indicating differential effects across exposures. LOAD3e4 is a novel strain developed to study genetic and environmental contributions to AD. Investigating how the exposome interacts with genetics may reveal mechanisms behind AD heterogeneity and identify intervention points. Preliminary results support studying toxic metal exposure during key developmental windows in LOAD mice. This work aims to clarify how these factors drive AD progression, advancing understanding and informing prevention and treatment strategies. Cohorts are on the shelf undergoing longitudinal phenotyping, with analyses ongoing.

Disclosures: Z. Sarica: None. K.P. Kotredes: None. O. Minaeva: None. J.A. Moncaster: None. S. Persohn: None. L. Ceotto Freitas Lima: None. A. Podder: None. D. Aylor: None. G.W. Carter: None. P.R. Territo: None. L.E. Goldstein: None. G.R. Howell: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.21/D24

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

Support: EXAF 100 PhDs for Africa Fellowship Grant

Title: Proteomic Profiling Identifies Serpin G1, ApoA-II, and LBP as Potential Biomarkers of Dementia in an Egyptian Cohort

Authors: *S. HEIKAL¹, M. SALAMA²;

¹The American Univ. in Cairo, Cairo, Egypt; ²The American Univ. of Cairo, Cairo, Egypt

Abstract: Introduction: Dementia, including Alzheimer's Disease (AD) poses significant public health challenge. Identifying specific biomarkers for the early detection of Dementia is crucial, for developing early diagnostic tools and targeted therapies. **Methods:** The present study performed proteomic profiling to identify serum biomarkers associated with Dementia in an Egyptian cohort. We analyzed 30 serum samples including patients and controls, recruited by the Egyptian Dementia Registry (EDN). **Results:** We identified 260 unique proteins, 21 were significantly differentially expressed between Dementia patients and controls ($p < 0.05$). Serpin G1 and LBP were downregulated, suggesting impaired regulation of inflammatory processes and compromised immune responses. ApoA-II was upregulated, indicating potential dysregulation in lipid metabolism. Enrichment analysis linked these proteins to pathways involved in inflammation, complement activation, and coagulation. **Conclusion:** This study provides the first proteomic characterization of an Egyptian Dementia cohort, identifying novel and established biomarkers associated with the disease and highlighting population-specific proteomic signatures.

Disclosures: S. Heikal: None. M. Salama: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.22/D25

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

Support: NIH/NIA RO1AG068293
Rainwater Foundation
Hevolution / AFAR
Cure Alzheimer's Fund

Title: Single-cell Spatial Multiomics Across Platforms Identifies a Novel Senescent Neuronal State, G_x, in Alzheimer's Disease

Authors: *T. ORR¹, L. WU³, A. HECK⁴, M. INGALLS⁵, A. NORTHCUTT⁶, O. BRAUBACH⁷, C. D. KEENE⁸, J. BEECHEM⁹, M. ORR²;

¹Washington Univ. Sch. of Med., Saint Louis, MO; ²Intrnl. Med., Washington Univ. Sch. of Med., St Louis, MO; ³Res. and Develop., ⁴Bruker Spatial Biol., Seattle, WA; ⁵Bruker Spatial Biol., Saint Louis, MO; ⁶Bruker, Billerica, MA; ⁷Canopy Biosci. - A Bruker Co., St. Louis, NV; ⁸Pathology, Univ. of Washington, Seattle, WA; ⁹Nanostring Technologies, Piedmont, CA

Abstract: Cellular senescence is a cell state characterized by apoptosis resistance, cell cycle arrest, and proinflammatory secretome. Senescent cells accumulate with aging, and their role in neurodegenerative diseases like Alzheimer's disease (AD) is increasingly recognized. However, senescent cells are challenging to study *in situ* due to their loss of cell identity, heterogeneous and complex cellular and molecular features. Here we used spatial proteogenomics to explore

postmortem human AD brains and identified a unique type of neuron, referred to as “neurescent”, that is arrested in a senescent-like cell state we refer to as “G_X”. We used the Digital Spatial Profiler platform for high-plex multiomic analyses of discrete regions of interest (ROIs) in formalin fixed paraffin embedded tissue sections while preserving spatial context. The assays use antibodies and *in situ* hybridization probes coupled to photocleavable DNA barcodes readout with NGS sequencing. We employed a stackable multi-omics platform including the Human Neural Proteome Atlas (500+ targets), Human Immuno-Oncology Proteome Atlas (570+ targets), an ultra-high-plex neural proteomic panel, and a Whole Transcriptome RNA panel. We examined cellular and molecular changes near and far from AD-associated amyloid and tau pathologies, as well as proteogenomic features of senescent cells, in postmortem hippocampal tissues from AD, age-matched controls, and young healthy controls. To validate candidate senescence-associated proteins, we used CellScape™, a high-resolution single-cell imaging platform that combines iterative immunofluorescence and automated analysis to quantify dozens of proteins with spatial resolution, including low-abundance targets often missed in other assays. We developed and applied a 31-plex panel on CellScape to assess G_X markers in serial tissue sections. Collectively, our multi-platform spatial analyses identify G_X neurescent cells as a novel senescent-like neuronal population enriched near AD neuropathology. These findings support G_X neurons as potential biomarkers and therapeutic targets for senolytic interventions currently under clinical evaluation for AD.

Disclosures: T. Orr: None. L. Wu: None. A. Heck: None. M. Ingalls: None. A. Northcutt: None. O. Braubach: None. C.D. Keene: None. J. Beechem: None. M. Orr: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.23/D26

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

Support: R01AG075820
RF1AG071587
R01 COA

Title: Age and Pathology dependent mechanisms and CSF Biomarkers of Cognitive Resilience

Authors: *U. SRIVASTAVA¹, S. RAYAPROLU³, A. TFAILY⁴, D. DUONG⁵, E. B. DAMMER⁶, N. T. SEYFRIED⁶, S. RANGARAJU²;

¹Dept. of Neurol., Yale Univ. Sch. of Med., new haven, CT; ²Neurol., Yale Univ. Sch. of Med., NEW HAVEN, CT; ³Neurol., Univ. of Florida, Gainesville, FL; ⁴Laney graduate school Emory Univ., Brookhaven, GA; ⁶Human Genet., ⁵Emory Univ., Atlanta, GA

Abstract: Chronic neurological diseases, regardless of pathological origin, converge on neurons, leading to synaptic dysfunction, neurodegeneration, and cognitive decline. Understanding

molecular pathways that confer resilience is essential for uncovering mechanisms that preserve neural function despite accumulating pathology. Through a proteome-wide association study (PWAS), we nominated 299 resilience-associated proteins and grouped them into mitochondrial, synaptic, and ribosomal sub-groups. We performed tandem mass tag mass spectrometry (TMT-MS) proteomics of brain wild type (WT), 5xFAD (amyloidosis; brain and CSF, age 1.8-14 months), and P301S (tauopathy; 3-9 months) mice to examine age and pathology specific resilience trajectories. In WT brains, mitochondrial resilience increased with age. In contrast, tauopathy showed declining mitochondrial resilience, progressive loss of synaptic resilience, and a biphasic ribosomal response initially increasing at 5 months before decreasing at 9 months. These patterns suggest that early compensatory responses ultimately fail as disease progresses. In 5xFAD brains, synaptic and ribosomal resilience declined with age, whereas mitochondrial resilience increased, indicating distinct compensatory adaptation due to amyloidosis. In tauopathy, resilience trajectories were more uniformly impaired: mitochondrial resilience remained low, synaptic resilience declined steadily, and ribosomal resilience showed transient compensation followed by breakdown. Compared to amyloidosis, tauopathy revealed more consistent loss of resilience proteins across all resilience sub-groups. Additionally, mitochondrial resilience proteins were significantly downregulated in ApoE4 as compared to ApoE3 knock-in brain. To assess how brain-based resilience mechanisms are reflected in the CSF, we performed TMT-MS on CSF obtained from our WT and 5xFAD aging cohort. Interestingly, age and amyloidosis-related changes in resilience proteins occurring in the brain did not mirror changes in the CSF. Brain-CSF co-expression analyses identified over 300 CSF proteins that were significantly correlated with brain resilience proteins, of which the majority were biomarkers of mitochondrial resilience. These CSF biomarkers of brain resilience were enriched in extracellular matrix and perineuronal net proteins (eg. Hapln2, Eml2, Colla1, Vcan, Ncan). In summary, this multi-model, cross-compartment analysis uncovers distinct molecular resilience trajectories shaped by aging, amyloidosis, tauopathy, and ApoE genotype. We also nominate CSF ECM proteins as biomarkers of resilience.

Disclosures: U. Srivastava: None. S. Rayaprolu: None. A. Tfamily: None. D. Duong: None. E.B. Dammer: None. N.T. Seyfried: None. S. Rangaraju: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.24/D27

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

Title: A Streamlined Approach for the Development of Spatial Biology Assays in Neuroscience

Authors: *M. H. INGALLS, C. E. JACKSON, B. LANE, X. MESHNIK, K. CASHION, A. J. NORTHCUTT, O. BRAUBACH;
Bruker Spatial Biol., Saint Louis, MO

Abstract: Implementing spatial biology workflows in neuroscience is a time and resource-intensive endeavor that relies on limited, high-value specimens and demands rigorous optimization to ensure specificity, sensitivity, and reproducible data. We previously demonstrated that the CellScape™ Precise Spatial Proteomics platform with EpicIF™ signal removal technology enables individual samples to be re-stained and imaged over a period of weeks to months with real-time adjustments of reagent panels.

Here, we present a streamlined low-risk workflow for the development of neuroscience multiplex immunofluorescence panels in as little 2 weeks by leveraging the real-time flexibility of the CellScape platform. We committed a single healthy control and an Alzheimer's diseased (AD) human formalin-fixed, paraffin embedded section (FFPE) for the initial screening of antibody clones for the study of neurodegenerative disease. To profile cell types of interest including neurons, glia, and vasculature, antibodies targeting biomarkers such as Map2, aSMA, GFAP, CD34, and Vimentin were first screened and optimized on the healthy control tissue. Neurodegenerative and stress markers like beta-amyloid and neurogranin were then applied on the same healthy section followed by the AD sample. All clones were assessed for sensitivity and specificity using our multiplex panel validation scoring system. Clones with the highest sensitivity and specificity scores across both diseased and control samples were included in the finalized neuro-spatial assay panel.

To ascertain the robust nature of this streamlined assay development process, the finalized panel was assessed for reproducibility by comparing specificity and sensitivity scores as well as spatial niche assessment by using cellular phenotype-based spatial neighborhood analysis across congruent regions on at least 3 serial sections of healthy control and AD FFPE tissue. Our results demonstrate that clones screened on a limited number of neural tissue samples with the same histological preparation can be compiled into a robust neuro-spatial assay panel to produce consistent results with limited sample availability in a short period of time.

Disclosures: **M.H. Ingalls:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. **C.E. Jackson:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. **B. Lane:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. **X. Meshik:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. **K. Cashion:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. **A.J. Northcutt:** A. Employment/Salary (full or part-time): Bruker Spatial Biology. **O. Braubach:** A. Employment/Salary (full or part-time): Bruker Spatial Biology.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.25/D28

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

Support: NIH Grant R01AG081374

Title: Clptm1 knockdown alters lipid storage and gene expression pathways linked to membrane regulation and alzheimer's disease

Authors: *E. BRANDT¹, H. ZHANG¹, C. THAPA², G. C. TRACY³, A. KOZLOVA⁴, J. DUAN⁵, A. SANDERS¹;

¹Endeavor Hlth. Res. Inst., Evanston, IL; ²Ctr. for Psychiatric Genet., Endeavor Hlth., Evanston, IL; ³Mol. and Integrative Physiol., Univ. of Illinois At Urbana-Champaign, Champaign, IL; ⁴NorthShore Univ. HealthSystem, Evanston, IL; ⁵NorthShore Univ. HealthSystem/University of C, Evanston, IL

Abstract: CLPTM1 (cleft lip and palate transmembrane protein 1) is a multi-pass transmembrane protein involved in GABAA receptor trafficking and membrane organization. Recent transcriptome-wide association studies (TWAS) have implicated CLPTM1 expression in Alzheimer's disease (AD) risk across multiple human neocortical regions. However, the overall biological function of CLPTM1 and its potential contribution to AD pathophysiology remain unclear. To investigate CLPTM1 function, we generated a CRISPR-Cas9 iSTOP knockdown in human-derived HEK293T cells and confirmed loss of CLPTM1 expression. All experiments were conducted with authenticated cell lines and included biological replicates to ensure reproducibility. Preliminary BODIPY staining revealed reduced lipid droplet accumulation and lower fluorescence intensity in CLPTM1-deficient cells, suggesting altered lipid storage or processing. Bulk RNA sequencing revealed coordinated downregulation of genes involved in cholesterol uptake (LDLR), efflux (ABCA1), and biosynthesis (HMGCR), along with repression of lipid-sensing regulators (e.g., GRAMD1A-C, INSIG1/2). These changes were accompanied by upregulation of ER stress and glycosylation-related genes, consistent with compensatory responses to disrupted membrane homeostasis. The observed reduction in lipid droplet accumulation was also supported by downregulation of HILPDA, a lipid droplet-associated protein involved in triglyceride storage under metabolic stress. Together, these transcriptional shifts suggest that CLPTM1 contributes to membrane lipid balance and stress adaptation, pathways known to be disrupted in AD. While the precise role of CLPTM1 in the brain remains to be defined, we are actively investigating its function in additional cell types relevant to AD. Together, our findings suggest CLPTM1 may contribute to the regulation of membrane lipid homeostasis and point to a potentially underappreciated mechanism in neurodegenerative disease.

Disclosures: E. Brandt: None. H. Zhang: None. C. Thapa: None. G.C. Tracy: None. A. Kozlova: None. J. Duan: None. A. Sanders: None.

Poster

PSTR012: Alzheimer's Disease: Omics Approaches I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR012.26/D29

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

Title: Bridging single-nucleus transcriptomic profiles with neural network functions and locomotor behaviors in an Alzheimer's Disease mouse model

Authors: *X. JIANG¹, J. PAN², P. HONMA³, J. SHIN⁴, R. THOMAS⁵, D. XIA⁶, I. COBOS⁷, J. J. PALOP⁸;

¹Gladstone Institutes, UCSF, San Francisco, CA; ²Pathology, Stanford Univ., Palo alto, CA;

³Neurosci. Grad. Program, UCSF/Gladstone, San Francisco, CA; ⁴Gladstone Inst. of Neurodegenerative Dis., ⁵Gladstone Inst., San Francisco, CA; ⁶Denali Therapeut., South San Francisco, CA; ⁷STANFORD UNIVERSITY, Stanford, CA; ⁸Gladstone Inst. & UCSF, San Francisco, CA

Abstract: Objective - Alzheimer's Disease (AD) is a neurodegenerative disease characterized by pathological protein deposit in the brain, including amyloid plaques and neurofibrillary tangles. AD patients show disease-associated transcriptomic alterations in a cell-type-specific manner and display aberrant brain network activities, which eventually leads to behavioral deficits. However, few studies have revealed the relationship between transcriptomic expression at single cell resolution, neural network dynamics, and behavioral activity.

Methods - To systematically investigate how variation in transcriptomic profiles interact with neural network dynamics, we performed single-nucleus RNA sequencing (snRNA seq) on dissected hippocampi sections from AD knock-in (App KI) mice (n=39) following 14-day continuous telemetric electroencephalography recording which includes a readout of mouse locomotor activity.

Results - We identified and quantified disease alterations in theta and gamma band power and detected multiple types of epileptiform spike activities in male and female KI mice, and we observed nocturnal locomotor hyperactivity specifically in female KI animals. Using the snRNA seq data, we found differentially expressed genes in major cell type including interneurons, oligodendrocytes, astrocytes, and microglia, corresponding to locomotive hyperactivity, gamma power alterations, and epileptiform spikes, and performed functional analysis to show potential proteomic pathways relevant to neural network dynamics.

Conclusions - Our study provides new insights on the mechanistic relationships connecting behavioral alterations, network dysfunction and transcriptomic variations, and may support the development of treatments for AD.

Disclosures: X. Jiang: None. J. Pan: None. P. Honma: None. J. Shin: None. R. Thomas: None. D. Xia: None. I. Cobos: None. J.J. Palop: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.01/D30

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

Support: The Garrison Family Foundation
Center of Excellence for Translational Neuroscience and Therapeutics,
TTUHSC

Title: Cerebellin1 modulates the autophagy pathway through GluD1 receptors in the J20 mouse model of Alzheimer's disease

Authors: *Y. CHEN^{1,2}, X. L. YIN¹, T. KIRITOSHI², M. MANCZAK^{1,3}, A. HINDLE¹, G. JI^{2,3}, V. NEUGEBAUER^{1,2,3};

¹Garrison Inst. on Aging, ²Dept. of Pharmacol. and Neurosci, ³Ctr. of Excellence for Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Cerebellin1 (Cbln1) is a secreted protein that links presynaptic neurexins to postsynaptic delta glutamate receptors, GluD1/GluD2, to form the trans-synaptic neurexin-Cbln1-GluD1/2 complex, which is important for synaptic organization and plasticity in the central nervous system. There is evidence for GluD1 to regulate autophagy, and autophagy is impaired in patients with Alzheimer's disease (AD) as well as in AD mouse models. We thus hypothesized that impaired Cbln1-GluD1 signaling in the J20 mouse model of AD is causally linked to impaired synaptic plasticity and autophagy, and restoring Cbln1 levels might ameliorate cognitive deficits observed in J20 AD mice through the modulation of the autophagy pathway. Accumulating evidence has shown that BDNF, an important contributor to synaptic plasticity, and mitochondrial superoxide dismutase 2 (MnSOD2) play an important role in regulating autophagy in the central nervous system. We measured the expression of BDNF, MnSOD2, and an autophagy marker protein (beclin 1) in the hippocampus of wild type (WT) and J20 mice (8 months old) using western blotting. Expression of BDNF, MnSOD2, and beclin 1 proteins was decreased significantly in J20 mice compared with WT mice. A single stereotaxic injection of recombinant human Cbln1 into the lateral ventricle blocked these changes. To explore if the GluD1 receptor is involved in the rescue effects of Cbln1, GluD1 siRNA or control non-target siRNA was injected into the lateral ventricle of J20 mice 2 days after the Cbln1 injection. BDNF, MnSOD2, and beclin 1 protein expression was measured in the hippocampus of these two groups of mice. Hippocampal expression of BDNF, MnSOD2, and Beclin 1 was lower in the GluD1 siRNA treated group compared to the non-target siRNA treatment group, suggesting that GluD1 receptors are involved in the beneficial effects of Cbln1 on the expressions of BDNF, MnSOD2, and beclin 1 protein in the J20 mouse model of AD. Together with our previous electrophysiological and behavioral data the results link the Cbln1-GluD1 complex to the modulation of the autophagy pathway in AD mice.

Disclosures: Y. Chen: None. X.L. Yin: None. T. Kiritoshi: None. M. Manczak: None. A. Hindle: None. G. Ji: None. V. Neugebauer: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.02/D31

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

Support: Garrison Family Foundation
Center of Excellence for Translational Neuroscience and Therapeutics,
TTUHSC

Title: Evidence for transsynaptic complex disruption in Alzheimer's disease patients

Authors: *A. HINDLE¹, Y. CHEN^{1,2}, X. L. YIN¹, M. MANCZAK^{1,3}, V. NEUGEBAUER^{1,2,3};
¹Garrison Inst. on Aging, ²Dept. of Pharmacol. and Neurosci., ³Ctr. of Excellence for
Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Approximately 7 million individuals in the United States are living with Alzheimer's disease (AD). Recent clinical progress has focused heavily on clearance of amyloid beta, but these therapies remain controversial and of limited efficacy. Consequently, there is a need for additional, novel therapeutic approaches. In addition to its hallmark amyloid plaques and neurofibrillary tangles, AD is characterized by synaptic dysfunction as well as impaired synaptic plasticity and autophagy, but functional mechanisms of synaptic changes and their relationship to AD pathology are not well understood. Transsynaptic complexes involving presynaptic neurexins (Nrxn1/2/3), secreted cerebellins (Cbln1/2/3/4), and postsynaptic glutamate delta receptors (GluD1/2) play critical roles in organizing synapses. These complexes strengthen and stabilize synaptic connections, mediate synaptic plasticity such as long-term potentiation, and regulate autophagy. In these complexes, secreted Cbln acts as a bridge between presynaptic Nrxns and postsynaptic GluD receptors. Recent studies in pain models have reported that treatment with recombinant Cbln1 can restore AMPA receptor balance and inhibit neuronal hyperexcitability and pain behaviors. Building on this, we hypothesized that similar dysregulation of Nrxn-Cbln-GluD transsynaptic complexes may occur in AD. To investigate this, we analyzed hippocampal tissue obtained from the Garrison Brain Bank and the NIH NeuroBioBank to compare protein and mRNA expression of transsynaptic complexes and autophagy-related pathways between early-stage AD, late-stage AD and non-AD individuals. At the protein level Cbln1, GluD2, and Beclin1 were significantly reduced in both early (Braak stage (BB) 2) and late-stage (BB5/6) AD relative to non-AD individuals ($p < 0.05$). GluD1 protein levels were significantly reduced only in early-stage (BB2) AD ($p < 0.05$), while p-cofilin and BDNF were specifically reduced in late-stage (BB5/6) AD ($p < 0.05$). qPCR analysis revealed a significant reduction in *GRID2* (GluD2) mRNA expression in late-stage AD (BB6) relative to early-stage AD (BB1/2) or non-AD individuals ($p < 0.05$), however no significant differences were observed for *NRXN1/2*, *CBLN1/2* or *GRID1* (GluD1). Collectively, these results suggest that homeostasis of molecules important for synaptic integrity and plasticity (Cbln-GluD transsynaptic complexes, BDNF, cofilin) is disrupted in both early and late-stage AD, with changes primarily occurring at the protein level. These alterations in transsynaptic complex expression are accompanied by the downregulation of autophagy regulators that are known to be linked to AD pathology.

Disclosures: A. Hindle: None. Y. Chen: None. X.L. Yin: None. M. Manczak: None. V. Neugebauer: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.03/D32

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

Support: R21 Grant AG085379
R01 Grant AG061800
NIA Grant AG068024
NIA Grant AG054719
U01 Grant AG061357

Title: A multi-network approach for identifying synaptic protein targets in Alzheimer's disease

Authors: *E. L. HOBBY¹, A. J. WEBER¹, N. T. SEYFRIED², J. H. HERSKOWITZ¹;
¹Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; ²Human Genet., Emory Univ., Atlanta, GA

Abstract: Proteomic studies can generate robust assessments that examine changes in protein abundances across different disease conditions, such as Alzheimer's disease (AD). These analyses can provide lists of various molecules altered in AD; however, identifying the individual proteins affecting specific biological processes remains a challenge. To address these hurdles, we used a multi-network approach to aid in the selection of protein targets from human brain proteomic datasets. Multiplex tandem mass tag mass spectrometry proteomic data (n = 8,212 proteins) was generated on human brain tissue from Brodmann area 46 dorsolateral prefrontal cortex. Samples were obtained from the Emory University Alzheimer's Disease Research Center (N = 41). These samples exhibit a range of AD pathology and are categorized into three diagnostic groups: controls, preclinical AD, and AD cases. In parallel, dendritic spine morphometry analysis was done on 443 neurons and 4,558 individual dendritic spines in the same individuals. Weighted gene co-expression network analysis (WGCNA) and SpeakEasy2 were used to construct networks of protein co-expression modules that were correlated with dendritic spine density and morphology. SpeakEasy2 module 3 negatively correlated with AD pathology and positively correlated with spine traits, and gene ontology analysis revealed that proteins in this module were critical for synaptic transmission. Additionally, WGCNA module 25 positively correlated with AD pathology and negatively correlated with spine traits, and gene ontology analysis demonstrated that these proteins were linked to synaptic signaling and membrane trafficking. These proteome network analyses could indicate key pathways involved in structural remodeling of dendritic spines in AD and help identify human proteins that are critical for synaptic biology and synapse loss in AD.

Disclosures: E.L. Hobby: None. A.J. Weber: None. N.T. Seyfried: None. J.H. Herskowitz: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.04/D33

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

Support: R21 Grant AG085379
R01 Grant AG061800
NIA Grant AG068024
NIA Grant AG054719
U01 Grant AG061357

Title: Alterations in dendritic spine morphology and tau phosphorylation in a humanized tau (hTau) mouse model

Authors: *J. M. EBERHARDT¹, E. L. HOBBY², K. M. GREATHOUSE², J. H. HERSKOWITZ²;
²Neurol., ¹UAB, Birmingham, AL

Abstract: Cognitive decline in Alzheimer's disease (AD) correlates most strongly with synapse or dendritic spine loss. In previous work, we identified an inverse relationship between dendritic spine density in the dorsolateral prefrontal cortex and tau pathology in AD. Here, we studied the relationship between tau phosphorylation (ptau) and dendritic spine density and morphology in a mouse model that expresses all six isoforms of human tau (hTau). We targeted individual layer II/III pyramidal neurons in the prelimbic medial prefrontal cortex (PFC) of 18, 21, and 24 month-old wild-type B6 and hTau mice for iontophoretic microinjection of fluorescent dye. High resolution confocal microscopy was used to image dendrites, followed by deconvolution and digital reconstructions for morphometric analysis of spines. We identified changes in spine volume and thin spine length at 18 and 21 months as well as decreased spine density in 24 month-old hTau mice, compared to wild-type controls. In parallel, synaptosome fractions were isolated from the PFC of similarly aged hTau cohorts, and ptau was measured by enzyme-linked immunosorbent assays. The levels of ptau increased with age, suggesting a link between changes in dendritic spine morphology and ptau at the synapse.

Disclosures: J.M. Eberhardt: None. E.L. Hobby: None. K.M. Greathouse: None. J.H. Herskowitz: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.05/D34

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

Support: "Finanziato dall'Unione europea – Next Generation EU – PNRR M6C2 - Investimento 2.1 Valorizzazione e potenziamento della ricerca biomedica del SSN". PNRR- MAD-2022-12376667; CUP: C53C22001550006

Title: Herpes simplex virus type-1 infection and its recurrent reactivations in the murine brain impair cognitive and motor functions correlating with EEG signatures: toward EEG based predictors of Alzheimer's disease

Authors: *C. FEROLETO^{1,2}, C. D'AMELIO², M. MOROTTI¹, I. PAOLETTI¹, C. CODAZZI², C. CALIGIURI², F. D'ALELIO¹, C. PAPPALETERA³, L. NUCCI³, F. FRASCA³, D. D. LI PUMA^{2,1}, G. DE CHIARA⁴, F. MIRAGLIA³, F. VECCHIO³, L. LEONE^{2,1}, C. GRASSI^{2,1}, M. V. PODDA^{2,1};

¹Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; ²Univ. Cattolica del Sacro Cuore, Rome, Italy; ³IRCCS San Raffaele, Rome, Italy; ⁴Inst. of Translational Pharmacol., Natl. Res. Council, Rome, Italy

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder marked by cognitive decline, memory impairment, and behavioral disturbances. To mitigate disease progression, the development of new, reliable tests is essential for detecting the initial signs of the pathology. Herpes simplex virus type-1 (HSV-1), a neurotropic virus capable of establishing latency within the central nervous system, has been linked to increased expression of pro-inflammatory cytokines and the exacerbation of AD-like pathology in both human and rodent brains. This study utilizes a mouse model of sporadic AD, induced by HSV-1 infection and recurrent reactivation through thermal stress (TS), to assess the progression of functional impairments and correlate them with electroencephalographic (EEG) alterations potentially predictive of AD pathology. Specifically, both memory and motor functions were evaluated and combined with in vivo EEG-like local field potential (LFP) recordings and immunohistochemical analyses of brain immune response to characterize the functional impact of HSV-1-induced inflammation on neural circuits. Mice subjected to two (2×TS) or seven (7×TS) thermal stress-induced HSV-1 reactivations, simulating initial stage and AD progression phenotypes, respectively, were tested in the Novel Object Recognition (NOR) and Y-maze tests for recognition and spatial memory assessment, respectively. Motor performance was assessed using grip strength and grid walking tests. Results indicated that after the second reactivation, both 2×TS and 7×TS HSV-1-infected mice exhibited a selective deficit in recognition memory in the NOR test compared to mock-infected mice. Notably, following the seventh reactivation, 7×TS HSV-1-infected mice demonstrated significant cognitive decline across all memory domains, including recognition and spatial memory, along with a pronounced neuroinflammatory profile. Regarding motor function, while no deficits were observed after the second TS, impairments were detected after the seventh TS in both grip strength and grid walking tests. More importantly, a significant reduction in forelimb force was evident following the fourth reactivation, suggesting a progressive impairment of motor circuits in AD prior to the worsening of the pathology. Functional deficits were accompanied by alterations in cortical connectivity, which manifested as early as the second reactivation, indicating that connectivity indices may serve as early biomarkers of disease onset and progression.

Disclosures: C. Feroletto: None. C. D'Amelio: None. M. Morotti: None. I. Paoletti: None. C. Codazzi: None. C. Caligiuri: None. F. D'Alelio: None. C. Pappalettera: None. L. Nucci: None. F. Frasca: None. D.D. Li Puma: None. G. De Chiara: None. F. Miraglia: None. F. Vecchio: None. L. Leone: None. C. Grassi: None. M.V. Podda: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.06/D35

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

Support: R01DA052271-05S1
R61AG086971-01A1

Title: Iqck, a novel alzheimer's disease risk gene, contributes to synaptic loss and memory deficits during aging

Authors: *J. AKKAOU¹, D. DEVADOSS¹, H. WANG², M. K. LAKSHMANA¹;
¹Herbert Wertheim Col. of Medicine, Florida Intl. Univ., Miami, FL; ²Inst. for Human Hlth. & Dis. Intervention (I-HEALTH), Florida Atlantic Univ., Jupiter, FL

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction, neuronal loss, and cognitive decline, particularly in aging populations. While current FDA-approved treatments offer limited efficacy, identifying novel genetic contributors to AD may reveal new therapeutic avenues. Genome-wide association studies have indicated several novel risk loci, including IQ-motif-containing protein K (IQCK), a gene of emerging interest in late-onset AD. To investigate IQCK's role as an AD risk factor, we employed a range of cellular models, including iPSC-derived neurons from fibroblasts of healthy controls and AD patients, primary neurons, synaptosomes, and newly developed IQCK transgenic mice. Our methodologies included proteomic analysis, immunoblotting, immunocytochemistry, and immunohistochemistry to uncover the mechanisms underlying IQCK's impact on AD pathology. Antibody-based microarray screening of 8,000 proteins revealed that IQCK significantly reduces amyloid precursor-like protein 1 (APLP1) levels and postsynaptic density protein 95 (PSD95), findings validated by immunoblots. These results were confirmed in multiple cell lines and in vivo using brain homogenates and synaptosomes from flag-IQCK transgenic mice. Interestingly, flag-IQCK transgenic mice showed heavily glycosylated form of IQCK, but when bred with 3xTg mouse model of AD, IQCK was completely deglycosylated. We are further exploring the significance of this effect on glycosylation. Importantly, behavioral assessments using T-maze indicated that aged (12-month-old) IQCK mice consistently and significantly made more errors over five days of training compared to their wild-type littermates. Moreover, the time taken to choose a goal arm was also significantly longer in IQCK mice, reflecting potential cognitive function impairment. Therefore, IQCK-mediated deficiencies in PSD95 may account for synaptic loss and the cognitive

impairments observed in AD, highlighting IQCK as a novel therapeutic target for future intervention. Further research is essential to clarify the specific mechanisms through which IQCK may contribute to synaptic dysfunction in AD.

Disclosures: J. Akkaoui: None. D. Devadoss: None. H. Wang: None. M.K. Lakshmana: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.07/D36

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

Support: Cure Alzheimer's Fund

Title: The role of Air Pollution in cognitive dysfunction and Alzheimer's risk

Authors: *X. CHEN;
USC, Los Angeles, CA

Abstract: Elevated air pollution (AirPoll) increases the risk of Alzheimer's disease (AD), but how AirPoll contributes to AD remains unclear. Neural stem cells (NSC), which decline with age and more rapidly in AD, often enter a state of quiescence, reducing their regenerative capacity and making them a key point of gene-environment (GxE) interaction. AirPoll exposure reduces NSC proliferation and increases amyloid peptides (A β 40 and A β 42), while the anti-amyloid drug BPN-15606 protects NSC from this damage. Thus I investigate two scientific questions: 1, whether normal age increase of A β is a mediator of NSC quiescence 2, if AirPoll-induced NSC quiescence is mediated by increased hippocampal A β . The study used Nestin-CFP transgenic mice to assess the impact of air pollution and BPN-15606 on neural stem cells in vivo. Mice were randomly assigned to filtered air (FA) or diesel exhaust particle (DEP) exposure, with each group further split to receive either BPN-15606 or vehicle control from 4 to 6 months of age. After treatment, some animals underwent single-cell RNA sequencing, while others were used for immunofluorescence (IF) analysis. scRNA-seq identified gene networks in NSC affected by AirPoll, providing a framework for evaluating the potential of BPN-15606 to mitigate environmentally induced AD risk. Differential gene expression analysis in the NSC cluster revealed that mice exposed to Airpoll exhibited upregulation of genes associated with gliogenesis compared to baseline. In contrast, mice exposed to both AirPoll and treated with BPN-15606 showed a partial restoration of neurogenic gene expression, suggesting a rescue of neurogenesis. IF assays showed that the total number of NSCs remained comparable between AirPoll -exposed and BPN-15606-treated groups. However, NSCs in AirPoll-exposed mice were more frequently activated, whereas BPN-15606 treatment led to an increased number of newborn neurons relative to baseline in each condition. Together, the scRNA-seq and IF data suggest that air pollution reduces neurogenesis by shifting NSC fate toward gliogenesis and increasing

quiescence. Mechanistically, these effects may be mediated by increased A β levels induced by AirPoll. These findings provide insight into how air pollution impacts human brain integrity at the molecular level and how they may contribute to the progression of AD. Further experiments are planned to investigate the potential of BPN-15606 to prevent A β plaque formation.

Disclosures: X. Chen: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.08/D37

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

Support: R01AG079257
R01DK093953
R01DK132088

Title: Sarm1 mediates synapse degeneration and memory loss in Alzheimer's disease

Authors: *F. FAN¹, P. JOSHI², X. LIU³, S. KOTTURU⁴, Q.-S. LIU³, X. LOU²;
²Dept. of Cell Biology, Neurobio. and Anat., ³Dept. of Pharmacol. and Toxicology, ¹Med. Col. of Wisconsin, Milwaukee, WI; ⁴Dept. of Cell Biology, Neurobio. and Anat., Med. Col. of Wisconsin, MILWAKEE, WI

Abstract: Synapse degeneration is a defining feature of Alzheimer's disease (AD) and represents the most reliable pathological correlate of cognitive decline. Compared to amyloid- β (A β) plaques and Tau tangles, synapse loss more accurately predicts cognitive impairment and disease onset, often preceding neuronal death and occurring decades before clinical diagnosis. Although A β has been shown to induce synaptic degeneration, the in vivo mechanisms remain poorly understood. Using a multidisciplinary approach, we investigated the molecular basis of synapse degeneration in 5xFAD mice---a widely used AD model harboring human familial AD mutations in amyloid precursor protein (APP) at three sites and presenilin-1 (PS1) at two sites. Our findings reveal that *Sterile alpha and TIR motif-containing 1* (Sarm1), an NAD⁺ hydrolase, plays a critical role in synaptic degeneration and contributes to AD pathogenesis. Sarm1 is an evolutionarily conserved member of the Toll/interleukin-1 receptor family, previously known for mediating Wallerian degeneration in the peripheral nervous system by initiating NAD⁺ depletion in damaged axons. In the central nervous system, we find that Sarm1 is enriched in presynaptic terminals, with pronounced accumulation in dystrophic axons and presynaptic terminals, particularly near amyloid plaques. Genetic deletion of *Sarm1* in 5xFAD mice significantly reduces synaptic dystrophy as compared to age- and sex-matched 5xFAD controls. Synapse loss in the CA1 hippocampal region is markedly attenuated, accompanied by suppression of complement cascade signaling and neuroinflammatory responses. Importantly, both short-term and long-term synaptic plasticity are fully restored by *Sarm1* deletion, along with a substantial

reduction in microglial activation and memory deficits. Our data support a model in which *Sarm1* mediates A β -induced synapse degeneration early in AD. Under A β stress, *Sarm1* activation initiates synaptic degeneration, which primes affected synapses for glia-mediated phagocytosis and drives a feed-forward cycle of glia activation, neuroinflammation, and exacerbation of A β pathology. Inactivation of *Sarm1* disrupts this pathogenic amplification loop, preserving synaptic integrity and function, protecting against memory impairment and cognitive decline. Collectively, these findings identify *Sarm1* as a central mediator of A β -induced synapse degeneration and disease progression. Targeting this pathway offers a promising therapeutic strategy to prevent synaptic failure and memory loss in Alzheimer's disease.

Disclosures: F. Fan: None. P. Joshi: None. X. Liu: None. S. Kotturu: None. Q. Liu: None. X. Lou: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.09/D38

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

Support: Institute for Basic Science (IBS-R025-A1)

Title: Inhibition of tau propagation by astrocytic synapse phagocytosis

Authors: *Y. CHOI^{1,2}, W.-S. CHUNG^{1,2};

¹Korea Advanced Inst. of Sci. and Technol., Yuseong-gu, Daejeon, Korea, Republic of; ²Ctr. for Vascular Research, Inst. for Basic Sci. (IBS), Yuseong-gu, Daejeon, Korea, Republic of

Abstract: In various tauopathies such as Alzheimer's disease (AD), hyperphosphorylated tau loses its ability to bind microtubules, resulting in the formation of somatodendritic and synaptic tau aggregates. In AD, these tau aggregates can propagate through synaptic connections, spreading from the entorhinal cortex (EC) to cortical area via the dentate gyrus (DG) of the hippocampus. While several mechanisms have been proposed for neuronal tau propagation, the roles of glia, especially astrocytes, remain unclear. Astrocytes, the most abundant cells in the brain, are closely associated with synapses and actively eliminating unnecessary synapses to maintain synaptic function and homeostasis during both developmental and adult stages. Since astrocytes have been shown to harbor tau aggregates in AD brains, we investigated the mechanisms and implications of tau uptake by astrocytes in neuronal tau propagation. To induce expression of human P301L mutant tau (hP301-Tau) in EC neurons and observe its propagation, we injected adeno-associated virus (AAV) encoding dual fluorescent protein-tagged hP301-Tau under the control of neuronal specific (human Synapsin) promoter. Importantly, we found that hP301-Tau propagated from EC to DG neurons, and was highly internalized by astrocytes, much more so than by microglia. Furthermore, hP301-Tau expression significantly enhanced astrocytic synapse phagocytosis, accompanied by upregulation of MERTK, a key phagocytic receptor

involved in synapse elimination. Surprisingly, hP301-Tau propagation from EC to DG neurons nearly doubled in astrocyte-specific *Mertk* knockout (*aMertk*KO) mice, while hP301-Tau uptake by astrocytes was significantly reduced. In contrast, astrocyte-specific knockdown of *Lrp1*, a previously suggested neuronal receptor for tau uptake, did not affect astrocytic tau uptake or tau propagation between neurons. This protective role of astrocytic MERTK was further confirmed by crossing PS19 tauopathy mice with *aMertk* KO mice, where *aMertk* KO exacerbated hippocampal tau accumulation. Together, these findings suggest that astrocytic synapse phagocytosis serves as a core mechanism for transferring tau from neurons to astrocytes, and that efficient astrocytic tau uptake can suppress neuronal tau propagation. Thus, we propose that enhancing astrocytic phagocytosis may be a promising strategy to mitigate tau spreading in neurodegenerative diseases.

Disclosures: Y. Choi: None. W. Chung: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.10/D39

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

Support: Larry L. Hillblom Foundation Fellowship 2021-A-012-FEL

Title: Delivery of astrocyte secreted Chrdl1 to target synapse loss in Alzheimer's disease

Authors: *A. DEREVYANKO¹, A. LEE¹, S. YIP¹, Q. ASBELL¹, S. ROBINSON¹, G. PULIATTI², N. J. ALLEN¹;

¹Salk Inst. for Biol. Studies, La Jolla, CA; ²Univ. Cattolica del Sacro Cuore, Rome.

Abstract: Dysfunction in synaptic AMPA glutamate receptors (AMPA Rs) underlies cognitive impairments observed in neurodegenerative disorders including Alzheimer's disease (AD). Deficits in AMPARs are attributed to the loss of synaptic GluA2 AMPAR subunits, which are calcium impermeable and present at mature, stable synapses. Therefore, targeting GluA2 loss can potentially counteract synaptic deficits and improve cognitive function that is impaired in AD. Astrocytes are glial cells that are essential for central nervous system function and play an important role in regulating synapse formation, function and stability through the release of secreted factors. Our group recently identified chordin-like 1 (Chrdl1) as a protein secreted by astrocytes that specifically promotes synaptic recruitment of GluA2-containing AMPARs and the formation of stable synapses in the brain. I developed a viral strategy to over-express Chrdl1 specifically in astrocytes in WT and AD mouse models. I then tested the potential of Chrdl1 to prevent or rescue disease progression by either over-expressing it before synapse loss occurred or by targeting synapses after mice already experienced synapse loss, respectively. I used the tauopathy Tau P301S (PS19) mouse model, which resembles the timeline of pathology progression in humans, including synaptic loss that precedes neurodegeneration. Chrdl1 over-

expression attenuated synapse loss and improved memory and cognitive flexibility in WT and Tau P301S (PS19) mice, highlighting its potential to improve function in AD and other disorders associated with excitatory synapse loss.

Disclosures: A. Derevyanko: None. A. Lee: None. S. Yip: None. Q. Asbell: None. S. Robinson: None. G. Puliatti: None. N.J. Allen: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.11/D40

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

Support: R01AG082362 (HNY, ZA)
P30AG066530 to HNY
P30AG066530 subaward (QLM)
R21AG089611(QLM)
P30AG066530 to USC Neuropathology Core,
R01AG070255 (AL)
P30AG10161 (ROS)

Title: Cytosolic phospholipase A2 mediates synaptic loss and cognitive dysfunction in Alzheimer's disease

Authors: *Q.-L. MA¹, B. E. KERMAN², B. LI⁵, S. WANG³, Z. ARVANITAKIS⁶, H. N. YASSINE⁴;

¹Keck Sch. of Medicine/University of Southern California, Los Angeles, CA; ²REMER, ³Keck Sch. of Med., ⁴USC, Los Angeles, CA; ⁵Keck Sch. of Med. of USC, Los Angeles, CA;

⁶Alzheimer's Disease Ctr., Rush Univ. Med. Ctr., Chicago, IL

Abstract: In Alzheimer's disease (AD), synapse loss is a key factor linked to cognitive decline. This loss has been associated with amyloid- β , tau pathologies, and neuroinflammation, however the initiating target remain elusive. Our study identified calcium-dependent cytosolic phospholipase A2 (cPLA2) as a significant synaptic target in AD. cPLA2 activation facilitates the conversion of membrane phospholipids into arachidonic acid (AA), which can be further metabolized into inflammatory eicosanoids. To investigate the role of cPLA2 in synapses within the human brain, we isolated synaptosomes from the postmortem frontal cortex of 60 participants with no cognitive impairment (NCI), mild cognitive impairment (MCI) and AD acquired from the Religious Orders Study. Total and phosphorylated cPLA2 isoforms were measured using Western blot, and compared with eicosanoid concentrations using targeted lipidomics. The interaction between cPLA2 and synaptic markers used immunofluorescent staining on human brain tissue and neurons derived from human induced pluripotent cells (iPSCs) treated with amyloid- β 42 oligomers (A β 42O). Our results indicated that cPLA2 α and cPLA2 β levels were

elevated in AD and showed an increasing trend in MCI. cPLA2 levels was correlated with increased postsynaptic density protein 95 (PSD-95) and cognitive dysfunction. AA and AA metabolites, such as TXB2 and PGF2 α , were increased in AD and correlated with cPLA2 levels, suggesting increased cPLA2 activity at synapses/synaptosomes. Phosphorylated cPLA2 α (p-cPLA2 α) colocalized with postsynaptic Ca²⁺/calmodulin-dependent protein kinase II α (CaMKII α), NMDAR subunits NR2A and NR2B, and dendritic microtubule-associated protein 2 (MAP2) in both NCI and AD brains. These synaptic and dendritic protein markers were locally reduced in AD. In neurons derived from human iPSCs, A β 42O treatment activated cPLA2 α , causing p-cPLA2 α to relocate from the cytosol to synaptic and dendritic sites, where it colocalized with CaMKII α and MAP2. Additionally, the levels of both CaMKII α and MAP2 were reduced at the synapses. These phenotypes were mitigated when using cPLA2 inhibitors. **These findings show** cPLA2 overactivation at synapses is associated with synaptic loss through the CaMKII α -PSD-95-NMDARs pathway, potentially contributing to cognitive decline in AD that can be mitigated using cPLA2 inhibitors.

Disclosures: Q. Ma: None. B.E. Kerman: None. B. Li: None. S. Wang: None. Z. Arvanitakis: None. H.N. Yassine: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.12/D41

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

Support: Albrecht Struppler Clinician Scientist Fellowship
DFG Grant

Title: Soluble TREM2 modulates neuronal activity through CD73

Authors: *F. UNGER^{1,3}, C. WOLF^{2,3}, N. ULMER², P. POUSINHA⁵, L. CHEN², P. ROSSIGNOL^{2,4}, C. GIUDICI⁶, A. EDER⁶, B. NUSCHER⁶, K. SCHLEPCKOW⁶, H. MARIE⁵, A. A. KONNERTH², C. HAASS⁷, M. WILLEM⁸, B. ZOTT³;

¹Inst. of Neuroscience, Tech. Univ. of Munich, München, Germany; ²Inst. of Neurosci., Tech. Univ. of Munich, Munich, Germany; ³Dept. of Neuroradiology, ⁴Dept. of Neurol., MRI Hosp. of the Tech. Univ. of Munich, Munich, Germany; ⁵Inst. de Pharmacologie Moléculaire et Cellulaire (IPMC), Valbonne, France; ⁶German Ctr. for Neurodegenerative Dis. (DZNE), Munich, Germany; ⁷Biochem., Ludwig-Maximilians-University Munich, Munich, Germany; ⁸Biomed. Ctr. (BMC), Fac. of Med., Ludwig-Maximilians-Universität München, Munich, Germany

Abstract: The triggering receptor expressed on myeloid cells 2 (TREM2) is an established risk factor for late-onset Alzheimer's disease (AD) and orchestrates the microglial response to plaque-induced pathology. Independent of AD pathology, TREM2 loss-of-function mutations increase seizure susceptibility in mice and humans, suggesting a broader role for TREM2, or its

shed ectodomain, soluble TREM2 (sTREM2), in regulating neuronal activity. To investigate this, we combined in vivo two-photon calcium imaging, pharmacology, electrophysiology, EEG, and microglial process tracking in wild-type, TREM2 knockout (TREM2^{-/-}), and TREM2^{H157Y} knock-in mice. The H157Y variant enhances sTREM2 shedding while reducing membrane-bound signaling.

TREM2^{-/-} mice exhibited elevated neuronal activity in the hippocampal CA1 region, while TREM2^{H157Y} mice showed reduced activity. Local injection of wild-type sTREM2 rapidly normalized hyperactivity in TREM2^{-/-} mice and suppressed activity in wild-type animals. In contrast, the sTREM2 disease variants sTREM2^{T66M} or sTREM2^{R47H} had minimal effects. Patch-clamp recordings revealed that sTREM2 reduced evoked postsynaptic currents in CA1 pyramidal neurons. Conversely, depleting extracellular sTREM2 using an antibody increased neuronal activity in wild-type and TREM2^{H157Y} mice, but not in TREM2^{-/-} animals. Mechanistically, sTREM2's effects depended on microglia, altered microglial surveillance, and a functional ATP-AMP-adenosine-A₁R signaling axis. sTREM2 bound to CD73, the enzyme converting AMP to adenosine, as shown by co-immunoprecipitation. Preincubation with inactive soluble CD73 blocked sTREM2-induced suppression of neuronal activity. Finally, mice with reduced or absent TREM2 expression were more prone to kainate-induced epileptiform activity, which could be rescued by enhancing adenosine signaling, suggesting a purinergic deficit in these models. In conclusion, sTREM2 modulates neuronal activity through CD73-dependent, purinergic microglia-neuron signaling. This mechanism may help counteract emerging neuronal dysfunction in early AD and - at least partially - explain why certain TREM2 mutations are associated with a higher AD risk.

Disclosures: F. Unger: None. C. Wolf: None. N. Ulmer: None. P. Pousinha: None. L. Chen: None. P. Rossignol: None. C. Giudici: None. A. Eder: None. B. Nuscher: None. K. Schlepckow: None. H. Marie: None. A.A. Konnerth: None. C. Haass: None. M. Willem: None. B. Zott: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.13/D42

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

Support: National Institute on Aging (NIA), National Institutes of Health (NIH), grant number K99AG065645, R00AG065645, R00AG065645-04S1, SARP mini grants TTUHSC EP, Edward N. & Margaret G. Marsh Foundation and TTUHSC EP MTM Startup Funds to SK

Title: Modulation of microRNA-502-3p significantly influences synaptic activity, dendritic spine density and mitochondrial morphology in the mice brain

Authors: ***B. SHARMA**¹, D. RODARTE², K. DONEPUDI², S. EADHA², G. GOYAL¹, R. A. PEREZ³, L. P. MONTES³, M. MIRANDA-ARANGO⁴, L. SÁNCHEZ SÁNCHEZ⁵, B. SALAMEH⁶, A. LIMON⁷, S. KUMAR²;

¹Mol. and Translational Med., Texas Tech. Univ. Hlth. Sci. Ctr. El Paso, EL Paso, TX; ²Mol. and Translational Med., Texas Tech. Univ. Hlth. Sci. Ctr. El Paso, EL Paso, TX; ³Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX; ⁴Dept. of Biol. Sci. and Border Biomed. Res. Ctr., Univ. of Texas at El Paso, El Paso, TX; ⁵Neurol. department, Univ. of Texas Med. Br. at Galveston, Houston, TX; ⁶Neurol. department, Univ. of Texas Med. Br. at Galveston, Houston, TX; ⁷Neurol. and Mitchell Ctr. for Neurodegenerative Dis., UTMB, League City, TX

Abstract: Synapse dysfunction is the root cause of Alzheimer's disease (AD). Uninterrupted and regulated synapse action is crucial to maintain healthy brain function. Our previous study discovered microRNA-502-3p (miR-502-3p), a synapse-specific miRNA, highly expressed at the AD synapses. Further, *in vitro* studies unveiled the biological relevance of miR-502-3p in modulating GABA receptor function, synaptic activity, and mitochondrial morphology. The current study focuses on investigating the role of miR-502-3p *in vivo* using stereotaxic injection of miR-502-3p overexpression (OE) and suppression (sponge) lentivirus (LV) into the hippocampus of C57BL/6 wild-type (WT) mice. MiR-502-3p OE and sponge LV were characterized by transducing HT22 cells followed by QRT-PCR and miRNAScope analysis of miR-502-3p. MiR-502-3p OE LV showed a very high-fold upregulation, and sponge LV showed a significant reduction in miR-502-3p levels. MiR-502-3p OE and sponge LV were injected into three-month-old WT mice brain hippocampus. Overexpression and suppression effects of miR-502-3p were studied on synaptic proteins, synapse number, mitochondrial morphology, and dendritic spine density at eight weeks post-injection. Mice injected with miR-502-3p OE LV showed reduced levels of synaptic proteins, diminished synapse formation, defective mitochondrial morphology, and reduced dendritic spine density relative to control LV-treated mice. While mice treated with sponge LV showed elevated levels of synaptic proteins, augmented synapses, improved mitochondrial morphology, and elongated dendrites and spine density. Our *in vivo* study unveiled translational abilities of miR-502-3p to restore synapse dysfunction in AD and other neurological disorders.

Disclosures: **B. Sharma:** A. Employment/Salary (full or part-time): Texas Tech University Health Science Center El Paso, Texas, USA. **D. Rodarte:** A. Employment/Salary (full or part-time): Texas Tech University Health Science Center El Paso, Texas, USA. **K. Donepudi:** None. **S. Eadha:** None. **G. Goyal:** None. **R.A. Perez:** None. **L.P. Montes:** None. **M. Miranda-Arango:** None. **L. Sánchez Sánchez:** None. **B. Salameh:** None. **A. Limon:** None. **S. Kumar:** A. Employment/Salary (full or part-time): Texas Tech University Health Science Center El Paso, Texas, USA.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.14/D43

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

Support: NIA-NIH Grant R01AG082147

Title: Kit signaling in neurogliaform cells regulates cortical inhibition and is disrupted in Alzheimer's disease

Authors: *J. SANZ-ROS¹, I. COBOS², A. SANKARAESWARAN³;

¹Dept. of Pathology, Stanford Univ. Sch. of Med., Stanford, CA; ²STANFORD UNIVERSITY, Stanford, CA; ³Stanford Univ., Palo Alto, CA

Abstract: Inhibitory dysfunction critically contributes to early cognitive decline in Alzheimer's disease (AD), yet the underlying cellular and molecular mechanisms remain unclear. Here, we identify a novel role for the receptor tyrosine kinase c-KIT in regulating the presynaptic structure and function of neocortical upper-layer neurogliaform cells (NGFCs), and demonstrate the disruption of c-KIT signaling in AD. We found that *KIT* expression is largely restricted to NGFCs in upper cortical layers, whereas its ligand (KITLG) is widely expressed in excitatory and inhibitory neurons within the same region. c-KIT localizes to presynaptic terminals, increases axonal bouton size upon activation, and enhances GABA release through local signaling. We show that neuronal activity drives KITLG translation and release from excitatory neurons. Furthermore, we demonstrate that the soluble ectodomain of c-KIT (s-KIT) is produced via metalloproteinase-mediated shedding from NGFCs and acts as a decoy receptor that binds free KITLG, limiting its binding to membrane-bound c-KIT. Increased s-KIT disrupts c-KIT signaling, inducing synaptic atrophy and lowering GABA release. In AD, s-KIT accumulates in the extracellular space and amyloid plaques, increasing with amyloid pathology in human tissue and a humanized AD mouse model. Notably, s-KIT also accumulates within astrocytes involved in blood-brain barrier maintenance, and CSF s-KIT levels correlated with amyloid- β_{42} and cognitive function. These findings uncover a novel, activity-coupled c-KIT signaling axis that regulates GABAergic synaptic function and suggest a neurodegenerative mechanism in which receptor ectodomain accumulation disrupts cortical inhibition in AD.

Disclosures: J. Sanz-Ros: None. I. Cobos: None. A. Sankaraeswaran: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.15/D44

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

Support: NIH/NCATS Colorado CTSA Grant (UL1 TR002535)
Boettcher Foundation's Webb-Waring Biomedical Research Program
BrightFocus Foundation
NIH grant (1R03AG072102)
Colorado State University

Title: Co-activation of selective nicotinic acetylcholine receptor subtypes is required to reverse hippocampal network dysfunction, fear memory loss, and amyloid pathology in Alzheimer's disease

Authors: *R. LEE¹, H. KIM¹, E. BLACK¹, S. KIM²;
²Biomed. Sci., ¹Colorado State Univ., Fort Collins, CO

Abstract: Alzheimer's disease (AD) is the most common form of dementia with no known cause and cure. Research suggests that a reduction of GABAergic inhibitory interneurons' activity in the hippocampus by beta-amyloid peptide (A β) is a crucial trigger for amyloid pathology and cognitive impairment in AD via hyperexcitability. Therefore, enhancing hippocampal inhibition is thought to be protective against AD. However, hippocampal inhibitory cells are highly diverse, and these distinct interneuron subtypes differentially regulate hippocampal inhibitory circuits and cognitive processes. Moreover, A β unlikely affects all subtypes of inhibitory interneurons in the hippocampus equally. Hence, identifying the affected interneuron subtypes in AD to enhance hippocampal inhibition optimally is conceptually and practically challenging. We have previously found that A β selectively binds to two of the three major hippocampal nicotinic acetylcholine receptor (nAChR) subtypes, α 7- and α 4 β 2-nAChRs, but not α 3 β 4-nAChRs, and inhibits these two receptors in cultured hippocampal inhibitory interneurons to decrease their activity, leading to hyperexcitation in excitatory neurons. We have also revealed that co-activation of α 7- and α 4 β 2-nAChRs is required to reverse the A β -induced adverse effects in hippocampal excitatory neurons. Here, we discover that α 7- and α 4 β 2-nAChRs predominantly control the nicotinic cholinergic signaling and neuronal activity in hippocampal parvalbumin-positive (PV+) and somatostatin-positive (SST+) inhibitory interneurons, respectively. Furthermore, we reveal that co-activation of these receptors is necessary to reverse hippocampal network dysfunction, amyloid pathology, and fear memory loss in the amyloid pathology model mice. This suggests that co-activation of PV+ and SST+ cells via stimulating α 7- and α 4 β 2-nAChRs together is a novel strategy for neuroprotection against AD.

Disclosures: R. Lee: None. H. Kim: None. E. Black: None. S. Kim: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.16/D45

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

Support: NIH Grant R01

Title: Excessive Alcohol Use Exacerbates Cognitive Deficits in an Alzheimer's Disease Mouse Model

Authors: *Y. GE;
Purdue Univ., West Lafayette, IN

Abstract: Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, characterized primarily by memory loss and cognitive impairment. Its pathological mechanisms are associated with amyloid-beta (A β) deposition, abnormal tau phosphorylation, and neuroinflammation. Recent reports have identified a history of alcohol consumption as a major risk factor for the onset and progression of AD. However, there is currently limited research on how alcohol dependence and excessive alcohol use affects progression of AD. In order to address this gap in the field, this study aimed to explore the impact of chronic excessive alcohol exposure on cognitive deficits associated with AD. We used 2-month-old APP/PS1 transgenic mice, a well-established mouse model of AD for testing. Male and female APP/PS1 mice (n=22) and their background controls (n=13) underwent two-bottle choice alcohol drinking (2BC) paired with chronic intermittent ethanol vapor exposure (CIE) for 7 cycles to develop alcohol dependence. In addition, a group of APP/PS1 mice (n=16) were given 2BC paired with air exposure during the CIE weeks. Alcohol-naïve APP/PS1 (n=20) and background mice (n=27; never exposed to alcohol) served as controls for behavioral testing. To assess cognitive performance at 8 months of age, we employed the Barnes Maze test and Novel Object Recognition (NOR) test. Behavioral data revealed that during the probe test of the Barnes Maze, both male and female APP/PS1 2BC/CIE exposed mice displayed significantly longer primary latency compared to APP/PS1 mice in the Air/2BC and alcohol-naïve groups, as well as significantly lower percent of target hole exploration, suggesting greater cognitive deficits. In the long-term memory test of the Novel Object Recognition task, both male and female APP/PS1 2BC/CIE exposed mice showed significantly reduced time exploring the novel object compared to Air/2BC and alcohol-naïve APP/PS1 mice, indicating more severe memory impairment. Together, the results from these two cognitive behavioral tests support our hypothesis that excessive alcohol use exacerbates cognitive deficits produced by AD pathology. Brain wide Fos activity associated with NOR and β -amyloid distribution in these mice is currently being assessed using iDISCO+. This will help identify key brain regions with disrupted neural activity during cognition compared to controls and what overlap, if any, exists with the neurological pathology of AD.

Disclosures: Y. Ge: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.17/D46

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

Title: Evaluation of the alterations in cholinergic neurotransmission in aging and amyloid precursor protein knock-in mice

Authors: *N. MATSUKAWA, I. NAGAI-ARAKAWA;
Nagoya City Univ., Nagoya-shi, Japan

Abstract: A progressive decline in cognitive function occurs as a result of Alzheimer's disease (AD) as well as aging, which is primarily associated with diminished cholinergic neurotransmission. However, the precise mechanisms contributing to cholinergic dysfunction are not fully understood. Herein, we evaluated the change of cholinergic system with age in wild type (WT) mice, and compared to those in AD-model (*App*^{NL-G-F}) mice with exhibiting overproduction of amyloid-beta 42 (A β ₄₂). In superfusion experiments, [³H]acetylcholine (ACh) release from the frontal cortex and hippocampal segments preloaded with [³H]choline exhibited no significant differences between adult (6-8 months old) and aged (12-17 months old) WT mice. Uptake of [³H]choline via the high-affinity choline transporter 1 (CHT1) and the subsequent formation/storage of [³H]ACh showed a moderate tendency to decrease associated with aging. In contrast, in *App*^{NL-G-F} mice, [³H]ACh release was significantly reduced in both the adult and aged groups, with reductions closely related to impaired CHT1 activity and diminished ACh synthesis/storage at cholinergic terminals. Presynaptic cholinergic feedback mechanisms regulating ACh release, as well as the density and subtype distribution of muscarinic ACh receptors were minimally affected by both aging and A β ₄₂ overproduction. These results support the A β hypothesis, suggesting that presynaptic cholinergic dysfunction arises early and is specifically caused by decreased CHT1 function in the AD forebrain, independent of age-dependent degeneration.

Disclosures: N. Matsukawa: None. I. Nagai-Arakawa: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.18/D47

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

Support: NIH RF1/R01AG072727
NIH RF1/R01AG069378
NIH U54GM128729

Title: Noradrenergic Dysfunction in AppNL-G-F Mice: Impaired Norepinephrine Metabolism and Compensatory Brain Changes in Alzheimer's

Authors: *N. KILIÇ¹, H. KAUR², C. K. COMBS³;

¹Univ. of North Dakota, Grand Forks, ND; ²Res., The Jackson Lab., Bar Harbor, ME; ³Dept of Biomed. Sci., Univ. of North Dakota Sch. of Med., Grand Forks, ND

Abstract: The locus coeruleus (LC) in the brainstem is the principal site of norepinephrine production in the brain. LC dysfunction has been linked to early stages of Alzheimer's disease (AD) although the underlying mechanisms remain poorly understood. In this study, we examined six-month-old male and female AppNL-G-F knock-in AD mice and wild-type controls to investigate LC integrity, norepinephrine metabolism, and compensatory brain changes. Despite a

significant reduction in hippocampal norepinephrine levels in both sexes of AppNL-G-F mice, tyrosine hydroxylase immunoreactivity in the LC demonstrated no apparent neuron loss. This suggested that the decreased hippocampal norepinephrine level was due to metabolic dysfunction rather than cell death. Interestingly, both sexes of AppNL-G-F mice exhibited higher protein levels of monoamine oxidase A (MAO-A), suggesting that increased norepinephrine turnover is responsible for the decrease in hippocampal levels. Immunohistochemistry demonstrated the expected neuronal immunoreactivity for MAO-A in hippocampi of both wild-type and AppNL-G-F mice. Surprisingly, total oxidase activity in the brains of both male and female AppNL-G-F mice was significantly reduced compared to their wild-type counterparts suggesting that MAO-A-specific activity assays will be required to directly correlate with the increased protein levels. To further evaluate compensatory responses to hippocampal norepinephrine levels, we assessed adrenergic receptor (AR) expression. Male AppNL-G-F mice exhibited increased α -1B AR levels, suggesting an upregulation of excitatory adrenergic signaling, whereas female AppNL-G-F mice displayed a reduction in α -2C AR levels, indicating a potential impairment in inhibitory adrenergic signaling. Both sexes showed elevated β -2 AR levels, reflecting a widespread compensatory response to norepinephrine loss. These findings highlight sex-specific differences in noradrenergic signaling, suggesting that males and females may experience distinct disruptions in NE function. Overall, our results reveal a previously unrecognized imbalance in norepinephrine metabolism in a common mouse model of AD, driven by MAO-A dysregulation rather than LC degeneration.

Disclosures: N. Kiliç: None. H. Kaur: None. C.K. Combs: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.19/D48

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

Support: Alzheimer's Association AARF-22-972333
NIH R01AG077692

Title: Inhibitory deficits in an Alzheimer's disease mouse model are accelerated by seizure induction

Authors: E. LANCASTER¹, K. F. HOAG², A. CHAVEZ³, D. M. TALOS⁴, *F. E. JENSEN³, A. J. BARBOUR²;

¹Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA; ²Neurol., ³Univ. of Pennsylvania, Philadelphia, PA; ⁴Neurol., Univ. of Pennsylvania, Perelman Sch. of Medicine, Philadelphia, PA 19104, Philadelphia, PA

Abstract: Neuronal hyperexcitability is being increasingly recognized as a critical factor in Alzheimer's disease (AD) progression. Indeed, seizures are present in up to 20% of Alzheimer's

disease patients and are associated with accelerated disease progression. In concordance, we have previously demonstrated that seizure induction exacerbates AD pathology and cognitive deficits. However, the effects of seizures on neuronal physiology in an AD model are underexplored. We hypothesized that seizure induction in prodromal amyloid precursor protein knock in (APPNLGF/NLGF) mice would worsen inhibitory function both acutely and at later disease stages. To test our hypothesis, we performed pentylenetetrazol seizure kindling or control, saline, protocols in 3-4 month old APPNLGF/NLGF and age-matched WT mice. Whole cell patch clamp was performed on slices 24 hours and 2-3 months following seizure induction to assess intrinsic excitability and inhibitory function. We found that APPNLGF/NLGF mice require significantly less PTZ administrations to induce tonic-clonic seizures ($p < 0.0001$, $n = 19-24$), corroborating our prior reports of increased seizure susceptibility in amyloidosis mouse models. 24 hours following seizure induction, we found no significant changes in action potential (AP) firing rate in response to current injection ($n = 3$ mice, 12-14 cells/group). We found reduced mini inhibitory post synaptic current (mIPSC) amplitude in PTZ kindled WT mice and Sal and PTZ treated APPNLGF/NLGF mice compared to WT/Sal ($p < 0.0001$, $n = 3$ mice/group, 12-14 cells/group) and increased mIPSC intervals in PTZ kindled APPNLGF/NLGF mice compared to all other groups ($p < 0.0001$, $n = 3$ mice/group, 12-14 cells/group), demonstrating early inhibitory dysfunction due to seizure induction in APPNLGF/NLGF mice. 2-3 months following seizure induction, we found no significant changes in AP rate in response to current injection ($n = 3$ mice/group, 18-23 cells/group). We also found reduced mIPSC amplitude in PTZ treated WT mice compared to all other groups ($p < 0.05$, $n = 3$ mice/group, 18-23 cells/group), and increased mIPSC intervals in PTZ treated WT mice and in Sal and PTZ treated APPNLGF/NLGF mice compared to WT/Sal ($p < 0.0001$, $n = 3$ mice/group, 18-23 cells/group), demonstrating inhibitory deficits in PTZ treated WT mice months following seizure induction and in 7 month old APPNLGF/NLGF mice, regardless of treatment. Together these data suggest that seizure induction accelerates inhibitory dysfunction in APPNLGF/NLGF mice. Thus, seizures are a promising target to mitigate neuronal inhibitory dysfunction in AD.

Disclosures: E. Lancaster: None. K.F. Hoag: None. A. Chavez: None. D.M. Talos: None. F.E. Jensen: None. A.J. Barbour: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.20/D49

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

Title: Identifying miRNA Networks Linking Cognitive Stimulation to Synaptic Function in Alzheimer's Disease

Authors: *M. LANZA¹, A. CACCAMO¹, S. ODDO¹, E. ESPOSITO²;

²Dept Chem. Biol. Pharmaceut. and Envrn. Scences, ¹Univ. of Messina, Messina, Italy

Abstract: Synaptic dysfunction and neurodegeneration are hallmarks of Alzheimer's disease (AD), leading to the progressive cognitive decline characteristic of the disorder. Given the lack of a cure and the limited effectiveness of available therapies, there is an urgent need to identify novel strategies that promote neuroprotection and synaptic plasticity. Environmental enrichment (EE) is a well-established approach that induces cognitive stimulation and enhances synaptic plasticity. Multiple studies have demonstrated that EE acts as a plasticity modulator in various conditions and experimental models. Indeed, EE has been shown to upregulate BDNF, synaptophysin, and PSD95, leading to improved synaptic function. However, the mechanisms linking EE to increased synaptic markers remain largely unknown. This study aims to evaluate how miRNA levels change following cognitive stimulation. Twelve-month-old APP/PS1 transgenic mice will be randomly assigned to either a naïve or an enriched group. The naïve group will be maintained in a standard housing environment, while the enriched group will be exposed to an enriched environment for four weeks, consisting of various interactive toys. After the enrichment period, each mouse's brain will be divided for analysis: one half will be used for full miRNA profiling via RNA sequencing, allowing us to identify miRNAs that change in an activity-dependent manner. The differentially expressed miRNAs will then be analyzed using bioinformatics tools to identify their target genes, with a primary focus on synaptic targets. The remaining half of the brain will be used for protein extraction and validation of bioinformatics predictions. Overall, we anticipate that our findings will uncover novel mechanisms linking cognitive stimulation to enhanced synaptic activity. These insights may help guide innovative therapeutic approaches to mitigate this debilitating disorder.

Disclosures: M. Lanza: None. A. Caccamo: None. S. Oddo: None. E. Esposito: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.21/D50

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

Support: NIH R01 AG063945
NIH R21 AG059223
Jeanna Kempner Fellowship (C.N.)
The Don and Nancy Mafrige Professor in Neurodegenerative Disease
Endowment

Title: Functional changes underlying a small-molecule inhibitor contributing to improved cognitive reserve and synaptic resilience.

Authors: *S. MOHANTY¹, K. RAMASWAMY², C. NATARAJAN³, M. MONTALBANO³, B. KRISHNAN⁴;

¹Univ. of Texas Med. Br. at Galveston, Galveston, TX; ²Univ. of Texas Med. Br., Houston, TX;

³Neurol., ⁴Dept. of Neurol., Univ. of Texas Med. Br., Galveston, TX

Abstract: Dendritic spines, crucial for synaptic plasticity, learning, and memory, are known to undergo significant loss in Alzheimer's disease (AD), contributing to cognitive impairment. Phospholipase D1 (PLD1), an enzyme implicated in diverse cellular processes including cytoskeletal modulation and vesicle trafficking, exhibits elevated expression in AD pathology. Previous work demonstrated that pharmacological inhibition of PLD1 using VU0155069 (VU01) ameliorated dendritic spine deficits specifically in the CA1 hippocampal region of 6- and 12-month-old 3xTgAD mice, models displaying progressive A β and tau pathology. This study expands upon those findings to provide a comprehensive assessment of PLD1 inhibition across multiple brain regions. Six- and twelve-month-old 3xTgAD mice received intraperitoneal injections of VU01 (1 mg/kg) or saline control every other day for one month. Brain tissues were subsequently processed using the FD Rapid GolgiStain kit, and dendritic spines were imaged via high-resolution microscopy (100X) and quantified using ImageJ across hippocampal (CA2, CA3, DG), cortical (V1, V2, A1, A2), and amygdala (LA, BLA, CeA) subregions. Results revealed a consistent trend of increased dendritic spine density in VU01-treated mice compared to saline controls across the diverse brain areas examined, apparent at both early and advanced stages of AD-like pathology. These findings suggest that inhibiting PLD1 provides widespread neuroprotection against spine loss, potentially conserving critical synaptic structures like memory-associated mushroom spines, thereby supporting cognitive reserve in AD.

Disclosures: S. Mohanty: None. K. Ramaswamy: None. C. Natarajan: None. M. Montalbano: None. B. Krishnan: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.22/D51

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

Support: NIH Grant R01 DC 019348

Title: Combined behavioral effects of genes associated with autism spectrum disorder and Alzheimer's disease in mice.

Authors: *K. NOUROZI¹, C. C. LEE²;

¹Comparative Biomed. science, Louisiana state university, Baton Rouge, LA; ²Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD) share unexpected yet profound symptoms. ASD is a neurodevelopmental disorder that arises in early childhood, primarily affecting social communication, cognition, and behavior. In contrast, AD is a progressive neurodegenerative disorder that impairs memory and executive function in older adults. Although these conditions manifest at opposite ends of the lifespan, they appear to share common mechanisms, including disrupted synaptic function, abnormal neuronal connectivity,

and dysregulated neurotransmitter systems. Both disorders are also associated with overlapping genetic risk factors and pathological changes, such as abnormal processing of amyloid precursor protein (APP). This study investigated whether a SHANK3B mutation, frequently implicated in ASD, exacerbate neurodegenerative changes in an APP knock-in (APP-KI) mouse model of AD. Behavioral assessments were conducted at 6 and 12 months of age using a battery of tests: Y-maze, open field, light-dark box, novel object recognition, social interaction, and tail suspension tests. These assays were used to evaluate spatial working memory, anxiety-like behavior, social behavior, and depression-like behavior. Both APP-KI and SHANK3B/APP mice exhibited social impairments, reduced novelty preference, and increased depression-like behavior, with deficits becoming more severe with age, which varied among the different genotypes. These findings suggest that synaptic vulnerabilities linked to ASD may accelerate AD-related cognitive and behavioral decline, underscoring the importance of early intervention strategies that target shared molecular pathways between neurodevelopmental and neurodegenerative disorders.

Disclosures: K. Nourozi: None. C.C. Lee: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.23/D52

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

Support: NIH Grant 3RF1AG079199-01S1

Title: Targeting the Few to Affect the Many: Dynorphin Neuron-Specific Tyrosinase Expression Induces Widespread LC Degeneration

Authors: *L. A. HASSANEIN;
Emory Univ., Atlanta, GA

Abstract: The locus coeruleus (LC), a major source of brain norepinephrine, is among the earliest regions to exhibit degeneration in neurodegenerative diseases such as Alzheimer's and Parkinson's. While the vulnerability of tyrosine hydroxylase-positive (TH⁺) neurons in the LC has been well-characterized, little is known about the role of less abundant neuronal subtypes, such as dynorphin-expressing cells, in disease-related pathology. Dynorphin neurons make up approximately 10% of the LC and are also found in surrounding regions, yet their contribution to LC dysfunction and neurodegeneration remains unclear. To investigate the impact of neuromelanin (NM) accumulation in this sparse neuronal population, we injected a Cre-dependent human tyrosinase (hTyr) AAV into the LC of Dynorphin-Cre male and female mice. A Cre-dependent EYFP virus was used as a control. We observed NM production and cell death within the LC, not only in dynorphin-expressing cells but also in adjacent TH⁺ and TH⁻ neurons, suggesting a broader vulnerability induced by localized NM buildup. These findings implicate

dynorphin neurons in mediating NM-associated toxicity and reveal a potential mechanism by which small neuronal subpopulations can influence LC-wide neurodegeneration.

Disclosures: L.A. Hassanein: None.

Poster

PSTR013: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease: *In Vivo* Models I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR013.24/D53

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

Support: NIH Grant RF1NS130881

Title: Neuronal Par3 Deficiency Drives Age-Dependent Behavioral and Lysosomal Defects

Authors: *R. TANG^{1,2}, H. ZHANG², M. SUN³;

¹Cell Biol. and Neurosci., ²Neurosci. and Cell Biol., Rutgers Univ., Piscataway, NJ; ³UMDNJ-RWJMS, Piscataway, NJ

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of hyperphosphorylated Tau protein and amyloid-beta (A β) in the brain, the underlying mechanisms driving pathogenesis remain largely unclear. Previous studies have revealed that the polarity protein Par3 is completely absent in the brain tissues of AD patients. Par3 is a highly conserved polarity protein that forms a complex with Par6, PKC, and Cdc42, playing critical roles in regulating cellular development across various organisms. In neurons, Par3 is essential for axonal and dendritic remodeling, contributing to neuronal morphogenesis, polarization, and migration during brain development. Synaptic dysfunction is a major cause of cognitive impairment in AD, and dendritic spine loss is closely associated with synaptic failure. In our study, conditional deletion of Par3 in mouse neurons led to age-dependent accumulation of A β and hyperphosphorylated Tau, which became more pronounced with aging. Behavioral analyses of Par3 knockout (KO) mice at different ages revealed striking age-related changes. In the Morris water maze test, 5-week-old Par3 KO mice exhibited enhanced learning and memory abilities compared to wild-type (WT) mice. However, by 6 months of age, the cognitive performance of Par3 KO mice was comparable to that of WT mice. Notably, in 12-month-old Par3 KO mice, learning and memory abilities showed a significant decline, particularly in female KO mice, suggesting an age-dependent loss of cognitive function. In the marble burying test, Par3 KO mice displayed enhanced digging behavior at 5 weeks and 6 months of age, with 6-month-old KO mice burying significantly more marbles than their younger counterparts. Interestingly, this hyperactivity diminished in 12-month-old KO mice, returning to WT levels, suggesting an age-dependent behavioral transition. Furthermore, in vivo experiments revealed that loss of Par3 increased lysosomal pH in neurons, as detected using a lysosomal pH-sensitive reporter. Lysosomal enzymes function optimally under acidic conditions, facilitating protein degradation and apoptosis initiation. The elevated lysosomal pH observed in Par3-

deficient neurons suggests impaired lysosomal function and reduced intracellular clearance capacity, potentially contributing to the accumulation of AD-related pathological proteins. Collectively, our findings provide novel insights into the role of Par3 in maintaining neuronal homeostasis and suggest that Par3 deficiency may promote AD-like pathology through age-dependent synaptic dysfunction and lysosomal impairment.

Disclosures: R. Tang: None. H. Zhang: None. M. Sun: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.01/D54

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

Title: Overlapping therapeutic interventions for Alzheimer's disease using antidiabetic drugs

Authors: *L. ZHANG;
WuXi AppTec, Qidong, China

Abstract: Evidence from clinical and molecular studies suggests that type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction, with a higher risk of developing neurocognitive disorders, including Alzheimer's disease (AD). Patients with type 2 diabetes exhibit elevated levels of advanced glycosylation end-product (AGEs), activating various signaling pathways through receptor for AGE (RAGE) and leading to enhanced oxidative stress and inflammation, which is a common dysregulated pathway shared by most of the comorbidities associated with AD. To explore the mechanisms underlying the association between AD and T2DM, we examined the therapeutic effects of the GLP-1 receptor agonist liraglutide on disrupted biological pathway and the RAGE inhibitor FPS-ZM1 on cognitive function and pathology of 5×FAD mouse model. Our results indicate that liraglutide improved the spatial learning and memory in 5×FAD mice, reduced the expression of A β and the phosphorylation of Tau protein. FPS-ZM1 also improved the spatial learning and memory in 5×FAD mice and reduced the overall activation of astrocyte and microglial cell, although no changes were observed in A β plaques. Furthermore, after inducing insulin resistance by injecting streptozotocin (STZ) into the lateral ventricle of 5x FAD mice, we observed a significant increase in A β plaque deposition and disruption of the insulin signaling pathway. Liraglutide alleviated these pathological manifestations of AD and the dysfunctional insulin-related signaling pathway, further indicating that liraglutide can mitigate AD pathology by ameliorating insulin resistance. These findings support overlapping therapeutic effects targeting RAGE and GLP-1 pathways using FPS-ZM-1 and liraglutide, suggesting beneficial potentials for diabetic patients diagnosed with AD.

Disclosures: L. Zhang: A. Employment/Salary (full or part-time): WuXi AppTec.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.02/D55

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

Support: NSERC Grant RG7441

Title: Metabolic disorders of the 5xFAD mouse model of Alzheimer's disease and the use of insulin as a therapeutic

Authors: *W. H. GENDRON¹, R. E. BROWN²;

¹Psychology and Neurosci., ²Psychology & Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: A subset of patients with Alzheimer's disease exhibit involuntary age-related weight loss not related to failure to eat. This weight loss can reduce the quality of life, increase frailty, and mortality. The 5xFAD mouse model of AD also exhibits this phenotype (Gendron, W. et al., 2021. Behav Brain Res, 406, 1-12.). The present study found that 12-month-old male and female 5xFAD mice tested in metabolic cages showed sex-specific metabolic abnormalities compared to WT mice (B6SJLF2/J). Both male and female 5xFAD mice exhibited weight loss, fat loss, and lean mass loss. In males this was driven by a hypermetabolic system, however, in females this weight loss was driven by a hypometabolic system that impaired activity, feeding behaviour, and fat production. Both AD patients and 5xFAD mice exhibit metabolic impairments in the brain such as reduced glucose metabolism (MacDonald, I., et al., 2014. Curr Alzheimer Res, 11, 450-460.). We therefore infused insulin intranasally and found that insulin infusions increased PI3K-Akt activation, improved spatial memory and muscle strength, and reduced frailty without inducing hypoglycemia. Insulin injections reduced freezing behaviour in the 5xFAD mice suggesting that this hormone may have anxiolytic properties. The results of these studies indicate that the 5xFAD mice exhibit metabolic impairment in the brain and body and the nature of this metabolic impairment is dependent on sex. Intra-nasal insulin enhanced the activation of the PI3K-Akt pathway thereby improving spatial memory and reducing frailty (Gendron, W., et al., 2024. Physiol Behav, 281, 1-16.). These studies support the hypothesis that AD is a metabolic disorder of the brain and body and indicate that the symptoms of this disorder may be partially reversed by hormones such as insulin that enhance Akt signalling and cognition.

Disclosures: W.H. Gendron: None. R.E. Brown: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.03/D56

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

Support: Intramural research funding

Title: Memantine enhances brain glucose uptake in mice through a gamma-secretase-dependent mechanism

Authors: A. FIDILIO¹, R. SANTANGELO¹, S. VARRASI¹, A. CACCAMO², F. CARACI¹,
*A. G. COPANI¹;

¹Drug and Hlth. Sci., Univ. of Catania, Catania, Italy; ²Chemical, Biological, Pharmaceut. and Envrn. Sci., Univ. of Messina, Messina, Italy

Abstract: Functional imaging studies indicate that reduced cerebral glucose metabolism precedes the onset of Alzheimer's disease (AD) (Reiman et al., *Proc. Natl. Acad. Sci. USA*, 2004). This metabolic impairment primarily affects the default-mode network (DMN), a region critical for maintaining attentional focus in young adults and one that accumulates β -amyloid ($A\beta$) deposits in older individuals with AD (Buckner et al., *J. Neurosci.*, 2005). The underlying cause of this metabolic deficit remains unknown. We aimed to test the hypothesis that neuronal glucose consumption during brain activation depends on the physiological release of $A\beta$. This idea stems from findings in neuronal cultures, where $A\beta$ monomers act as positive allosteric modulators of insulin-like growth factor-1 receptors (IGF-1R), regulating glucose uptake and aerobic glycolysis (Giuffrida et al., *Front. Cell. Neurosci.*, 2015; Santangelo et al., *Aging*, 2021). To assess the relevance of this mechanism in vivo, we examined glucose utilization in 10-12-week-old female mice following a pharmacological challenge with memantine, a clinical-stage NMDA receptor antagonist that enhances neuronal activity by inhibiting GABAergic transmission (Dedeurwaerdere et al., *Psychopharmacology*, 2011). First, we demonstrated that, in primary pure neuronal cultures, a 15-minute treatment with 1-10 μ M memantine stimulated glucose uptake—an effect blocked by pretreatment with the γ -secretase inhibitor DAPT (100 nM). For in vivo studies, fasted mice received subcutaneous injections of either vehicle or DAPT (100 mg/kg) 3 hours before saline or memantine (20 mg/kg). Subsequently, mice were administered the metabolic tracer 2-deoxyglucose (2-DG; 3 mg/kg, s.c.) and euthanized 1 hour after saline or memantine treatment. Quantitative analysis of 2-DG uptake in the prefrontal cortex revealed that memantine significantly enhanced glucose utilization compared to vehicle. This memantine-induced metabolic activation was attenuated by ~50% following DAPT pretreatment, suggesting that γ -secretase-dependent $A\beta$ release serves as a physiological regulator of neuronal glucose metabolism.

Disclosures: A. Fidilio: None. R. Santangelo: None. S. Varrasi: None. A. Caccamo: None. F. Caraci: None. A.G. Copani: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.04/D57

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

Support: Neuroscience Program, the Office of Research and Graduate Studies, College of Medicine, the John G. Kulhavi Professorship in Neuroscience, and the E. Malcolm Field and Gary Leo Dunbar Chair in Neuroscience at Central Michigan University.

Title: Effects of Liraglutide on Early Cognitive and Anxiety-Related Behaviors in 5xFAD and STZ-Induced Models of Alzheimer's Disease

Authors: *G. TAVI^{1,5,6}, D. DOYLE^{1,5,6,7}, O. SMITH^{2,5,6}, L. GARMO^{3,5,6,7}, J. ROSSIGNOL^{4,5,6,7}, G. L. DUNBAR, Sr.^{8,5,6,9};

¹Central Michigan Univ., Mt Pleasant, MI; ²Central Michigan Univ., Mount Pleasant, MI;

³Central Michigan Univ., Farmington Hills, MI; ⁴Col. of Med., Central Michigan Univ., Mount Pleasant, MI; ⁵Field Neurosciences Inst. Lab. for Restorative Neurol., Mt Pleasant, MI; ⁶Program in Neurosci., Mt Pleasant, MI; ⁷Col. of Med., Mt Pleasant, MI; ⁸Psychology/Program in Neurosci., CENTRAL MICHIGAN UNIVERSITY, MOUNT PLEASANT, MI; ⁹Dept. of Psychology, Mt Pleasant, MI

Abstract: Emerging evidence indicates that the glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide (LIR), exhibits neuroprotective properties in preclinical models of Alzheimer's disease (AD), potentially through modulation of insulin signaling and attenuation of neuroinflammatory processes. The present study sought to evaluate the effects of LIR on early behavioral outcomes in both 5xFAD transgenic mice and a non-transgenic model of sporadic AD (SAD), generated through intracerebroventricular administration of streptozotocin (STZ), a compound known to induce central insulin resistance and AD-like neuropathology. Forty-eight three-month-old 5xFAD and wild-type (WT) mice received bilateral intracerebroventricular injections of STZ or saline vehicle and were subsequently treated with LIR (25 nmol/kg, intraperitoneally) or vehicle daily for 30 days. Behavioral assessments included the open-field and passive-avoidance tasks, designed to evaluate locomotor activity, anxiety-related behavior, and associative memory. At this prodromal stage, LIR administration did not elicit robust effects across behavioral measures. However, subtle trends are being further explored in conjunction with ongoing biochemical and histopathological analyses, including Western blotting and immunohistochemistry targeting key markers of insulin signaling (e.g., p-Akt/Akt, p-GSK3 β /GSK3 β), amyloid burden, and neuroinflammation within the cortex and hippocampus. Preliminary findings suggest that behavioral impairments may not fully manifest at this stage, and that LIR may influence underlying neuropathology before overt deficits emerge, warranting further investigation into its temporal efficacy and potential as a prophylactic therapeutic in AD models.

Disclosures: G. Tavi: None. D. Doyle: None. O. Smith: None. L. Garmo: None. J. Rossignol: None. G.L. Dunbar: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.05/D58

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

Support: ANPCYT- UBA – CONICET
Baron Foundation
Fiorini Foundation
Williams Foundation

Title: Amyloid Beta Modulates Astrocyte Activation, Glucose Metabolism, and Insulin Pathways: Implications for Alzheimer's Disease

Authors: *M. I. M. BENTIVEGNA¹, J. BEAUQUIS²;

¹Biol. Chem., Inst. of Biol. and Exptl. Med. (IBYME-CONICET), Ciudad de Buenos Aires, Argentina; ²Inst. De Biología Y Medicina Experimental, CONICET, Buenos Aires, Argentina

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia. Beyond amyloid beta (A β) and tau aggregation, inflammation and insulin resistance are also frequent in AD brains. Astrocytes are crucial in maintaining homeostasis and managing inflammatory responses. This study aimed to 1) examine the metabolic and inflammatory status of PDAPP-J20 transgenic (TG) mice, an AD model, and 2) assess inflammatory activation, energy metabolism, and insulin signaling in astrocytes in vitro after A β exposure. We hypothesized that A β -treated astrocytes adopt a proinflammatory phenotype and lose homeostatic functions. Our findings revealed impaired insulin signaling (pAkt/Akt) in the hippocampus (p<0.05), along with reduced hippocampal insulin receptor (IR) levels (p<0.05). Immunolabeling for IR showed a decrease in GFAP+ astrocytes, which also displayed increased GFAP and S100b labeling (p<0.05), indicating proinflammatory reactivity. In vitro, A β exposure led to increased NF κ B nuclear translocation, elevated S100b (p<0.0001), and decreased EAAT2 expression (p<0.0001). Western blot and immunofluorescence analysis showed higher IR expression and increased membrane localization (p<0.05) in A β -exposed astrocytes. However, insulin-prompted IR phosphorylation decreased and Akt phosphorylation remained unchanged after A β exposure. A β -exposed astrocytes also showed increased glucose uptake (p<0.05) and a trend towards higher lactate production and glycogen accumulation (p<0.05). Additionally, the number of mitochondria decreased, while superoxide production increased (p<0.001). Despite reduced lipid droplet density, their colocalization with mitochondria increased (p<0.01), suggesting a metabolic shift towards β -oxidation. These results suggest that hippocampal insulin resistance and glial reactivity are concurrent in experimental AD. A β -exposed astrocytes adopt a proinflammatory phenotype with impaired insulin signaling and mitochondrial dysfunction, providing insight into AD pathophysiology.

Disclosures: M.I.M. Bentivegna: None. J. Beauquis: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.06/D59

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

Support: NIH Grant 1RF1AG082388-01

Title: Impact of Peripheral, Direct AMPK Activation in an Alzheimer's Disease Mouse Model

Authors: *N. I. NICOL¹, T. MA²;

¹Wake Forest Univ., Winston-Salem, NC; ²Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Alzheimer's disease (AD) is the most common form of dementia in the elderly, currently affecting over 37 million people worldwide. Despite extensive research, there is still no cure for AD. AD has been described as an energy crisis, with metabolic dysfunction occurring years before the onset of clinical symptoms. Numerous clinical trials focus on investigating metabolic-related interventions including exercise, caloric restriction, and the diabetes drug metformin. Notably, all these interventions are known to activate, indirectly, AMP-activated protein kinase (AMPK), the master regulator of cellular energy homeostasis. Moreover, previous studies have reported contradictory findings regarding AMPK's role in AD. This study seeks to clarify the effects of AMPK activation on AD by using MK-8722, a direct, pan-AMPK activator administered peripherally. Notably, MK-8722 is unlikely to cross the blood brain barrier, helping to reduce confounding factors from earlier studies. We administered 10 mg/kg/day of MK-8722 or placebo for 30 days via subcutaneous pellet placement in male and female wild-type (WT) and the APP/PS1 (APP) model of AD mice (6-8 months old; n = 13-15 per group). Mice underwent a series of behavioral tests including Novel Object Recognition (NOR), Y-maze, and Morris Water Maze (MWM). Preliminary results indicate a significant impairment in spatial memory in APP vehicle mice, as measured by reduced time spent in the target quadrant of MWM (p = 0.008 vs. WT vehicle). Importantly, this deficit was rescued with MK-8722 treatment (p = 0.011 vs. APP vehicle; p = 0.98 vs. WT vehicle). There were no changes in NOR between groups (p > 0.8 for all groups), suggesting that at this age, recognition memory is intact in the APP mice and unaffected by the drug in either genotype. Brain and liver tissues were collected after behavioral tests for biochemical analysis. In the liver, MK-8722 significantly activated AMPK in both genotypes (p = 0.004 WT vehicle vs. WT drug; p = 0.004 APP vehicle vs. APP drug). However, there was no change to AMPK activation in the hippocampus, suggesting that it does not cross the blood brain barrier at a sufficient level to activate (p > 0.7 for all groups). Statistical analyses were performed using two-way ANOVAs followed by Tukey's post hoc tests. These findings suggest that peripheral activation of AMPK by MK-8722 can restore spatial memory performance in APP mice to a level comparable to WT controls. Ongoing work is focused on elucidating the underlying mechanisms, with a focus on synaptic plasticity-related changes.

Disclosures: N.I. Nicol: None. T. Ma: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.07/D60

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

Support: NIH U24DK115255
NIH R01DK130913
the Sinai Medical Staff Foundation
the Robert E. Niderlander Sr. Program for Alzheimer's Research
the Andrea and Lawrence A. Wolfe Brain Health Initiative Fund
the NeuroNetwork for Emerging Therapies
NIH P30DK020572

Title: Potential Role of miR-223-3p in Connecting Insulin Resistance and Alzheimer's Disease via Extracellular Vesicle-Mediated Transfer

Authors: *B. KIM¹, E. L. FELDMAN²;

¹Univ. of Michigan, Ann Arbor, MI; ²Dept. of Neurol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Metabolic syndrome (MetS) and Alzheimer's disease (AD) share several pathological features, including insulin resistance, aberrant protein processing, mitochondrial dysfunction, and heightened inflammation and oxidative stress. MetS increases the risk of developing AD, though the precise molecular mechanisms remain unclear. A diet rich in sugars and saturated fatty acids, such as palmitate, promotes insulin resistance—a shared hallmark of both MetS and AD. Extracellular vesicles (EVs), known for their role in intercellular communication and disease propagation, also exhibit altered dynamics in both conditions. Here, we demonstrate that EVs derived from palmitate-treated oligodendrocytes (ODs) induce insulin resistance in recipient neurons and impair neurogenesis. These EVs (palEVs) carry bioactive cargo including RNAs, proteins, and metabolites. Analysis of miRNA profiles revealed that miR-223-3p is among the most differentially regulated microRNAs in palEVs compared to control EVs (ctlEVs). miR-223-3p levels are reduced in type 2 diabetes (T2D) mouse models and circulating EV-transported miR-223-3p levels predict progression of patients from prediabetes to T2D. Similarly, serum and EV-associated miR-223-3p levels decline progressively in AD patients and correlate positively with Mini-Mental State Examination scores. Our findings confirm that palmitate reduces miR-223-3p levels in OD-derived EVs. Neurons treated with either palEVs or a miR-223-3p inhibitor exhibit mitochondrial dysfunction and induced a decreased response of Akt phosphorylation—both markers of neuronal insulin resistance. Together, these results suggest that in the context of MetS, EV-mediated depletion of miR-223-3p disrupts neuroglial communication, promoting insulin resistance and mitochondrial dysfunction in neurons, and thereby increasing susceptibility to AD.

Disclosures: B. Kim: None. E.L. Feldman: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.08/D61

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

Support: UAB Nathan Shock Center P30AG050886
R56AG060959
I01 BX-004251-01

Title: Changes in Mitochondrial Electron Transport Chain Complexes Expression in Postmortem Human AD Brain

Authors: *S. BALASUNDARARAJAN;
Univ. of Alabama at Birmingham, Vestavia Hills, AL

Abstract: Alzheimer's disease (AD) is the leading cause of dementia, affecting an estimated 6.9 million Americans aged 65 and older. Mitochondrial dysfunction has been implicated as a key contributor to AD pathogenesis. The mitochondrial electron transport chain (ETC), composed of five complexes, is essential for ATP production via oxidative phosphorylation. Prior studies have reported alterations in ETC complex function in AD brains, resulting in disrupted energy metabolism and elevated oxidative stress. This study investigates protein expression changes in ETC complexes between AD and non-disease (ND) controls using postmortem human brain tissue from multiple Brodmann areas, in collaboration with various institutions: Emory University (BA8.9), UC Irvine (BA17, BA22, BA28), the University of Alabama at Birmingham (BA22), and the University of Washington (BA22). Using Western blot analysis, we observed significant reductions in the protein expression of complexes III and IV in AD brains compared to ND controls in the Emory samples (BA8.9). In contrast, UAB's Brodmann Area 22 samples exhibited no statistically significant changes. Sex-based comparisons revealed an increase in complex II expression between male ND and male AD samples in UAB (BA22); however, no other significant sex-based differences were observed in either sample. A broader analysis incorporating additional Brodmann areas will offer deeper insight into the regional variability of mitochondrial dysfunction in Alzheimer's disease, highlighting the spatial impact of AD on the brain. These findings advance our understanding of mitochondrial contributions to AD pathology and may inform the development of targeted therapies aimed at restoring mitochondrial function in affected brain regions.

Disclosures: S. Balasundararajan: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.09/D62

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

Title: Investigating mitochondrial resilience in asymptomatic Alzheimer's disease using systems biology approaches

Authors: *P. MANDAL, P. BALONI;
Purdue Univ., West Lafayette, IN

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder marked by cognitive decline, protein misfolding, and neuronal loss. Mitochondrial dysfunction plays a critical role in AD progression due to the brain's high energy demands. However, how mitochondrial function differs in the resilient or asymptomatic individuals with AD pathology remains poorly understood. To answer this question, we analyzed mitochondrial adaptations using data from three large scale cohorts across the USA such as ROS/MAP (Religious Orders Study/ Memory and Aging Project), Mayo clinic, and MSBB (Mount Sinai Brain Bank). The study included individuals clinically diagnosed with AD (n = 182) and an "asymptomatic-AD" group (n = 200) with similar levels of amyloid and tau pathology but preserved cognition (Mini Mental State Examination > 24). We integrated proteomics, bulk and single-nucleus transcriptomics from four brain regions—prefrontal (BA9), premotor (BA6), temporal (BA37), and hippocampus (BA36) across neuronal and glial cell types to identify mitochondrial pathways linked to resilience. Our analysis reveals cohort-specific differences in mitochondrial energetics. In the AD group, the prefrontal cortex exhibits downregulation of oxidative phosphorylation, branched-chain amino acid and fatty acid oxidation pathways consisting of *NDUFA2*, *PCCA*, *CPT1A* proteins, alongside dysfunction in all four electron transport chain complexes. In contrast, these pathways remain largely preserved in the asymptomatic group, indicating potential protective metabolic adaptations. At a cell-type level, inhibitory neurons in AD exhibited downregulation of mitochondrial genes such as *NDUFA4*, *ATP5MC1*, and *SLC25A5*, suggesting energy deficits, while excitatory neurons upregulated fatty acid metabolism genes like *CPT1B* and *ACACB*, indicating a shift in energy production. By integrating multi-omics data across brain regions and neuronal subtypes, we demonstrate that asymptomatic individuals maintain mitochondrial function despite comparable levels of amyloid and tau pathology, suggesting the presence of protective bioenergetic adaptations. The differential regulation of oxidative phosphorylation and fatty acid metabolism pathways across inhibitory and excitatory neurons highlights cell-type specific vulnerabilities and compensatory responses. These findings provide a systems-level understanding of mitochondrial dynamics in AD progression and resilience, offering potential targets for therapeutic intervention aimed at preserving cognitive function by sustaining neuronal energy homeostasis.

Disclosures: P. Mandal: None. P. Baloni: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.10/D63

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

Support: NIH Grant OD032451
NIH Grant OD035392
NIH Grant EY030747
NIH Grant EY031248

Title: Oxidative stress differentially affects the expression levels of proteins controlling mitochondrial and metabolic function in neural progenitor cells and neurons derived from neural progenitor cells depending on differentiation status.

Authors: R. S. DUNCAN, S. M. RIORDAN, *P. KOULEN;
Univ. of Missouri - Kansas City, Kansas City, MO

Abstract: Neural progenitor cells (NPCs) and NPC-derived neurons are increasingly used as *in vitro* model systems of neuronal metabolism and neurodegeneration. Oxidative stress occurs in most, if not all, neurodegenerative diseases which prompted us to determine whether oxidative stress differentially affected the proteomes of immature and differentiated NPCs. We exposed both undifferentiated and differentiated NPCs to *tert*-butyl hydroperoxide (tBHP, 10 μ M) for 24 hours. Using a proteomics approach, we identified differential protein expression among experimental groups based on cellular differentiation status, oxidative stress, or both. Enriched biological process pathways identified with this approach included iron-sulfur cluster assembly (1.3-fold, $p < 0.01$), negative regulation of programmed necrotic cell death (1.3-fold, $p < 0.05$), and metal ion transport (0.92-fold, $p < 0.05$), all of which implicate mitochondrial function. Within a proteome of 7,538 proteins, 190 proteins with significantly altered abundance compared to control were associated with mitochondrial structure and or function, at least 15 of these proteins were differentially expressed based on differentiation status. In addition, the cellular responses to oxidative stress were dependent on the differentiation status. Oxidative stress altered the expression levels of 24 proteins involved in mitochondrial structure or function in undifferentiated NPCs, while in differentiated cells, it altered the expression of 5 mitochondrial proteins. Of the 35 total differentially expressed proteins regulated by differentiation status or oxidative stress, 8 proteins were differentially regulated by both. Our results identify novel proteins regulated by the differentiation status of NPCs and in the response to oxidative stress. Changes in neuronal protein expression levels identify potentially novel therapeutic targets for the prevention and treatment of neurodegeneration and indicate novel effects with potential relevance to cytotherapies.

Disclosures: R.S. Duncan: None. S.M. Riordan: None. P. Koulen: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.11/D64

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

Support: Gutenberg Academy Fellows Program

Title: Contribution of nuclear-encoded precursor protein mitochondrial transport to the development of Alzheimer's disease

Authors: *J. BRECHTEL¹, M. JOERG², K. FRIEDLAND³;

¹Inst. of Pharmaceut. and Biomed. Sciences, Johannes Gutenberg Univ. Mainz, Mainz, Germany;

²Pharmacol. and Toxicology, Johannes Gutenberg Univ., Mainz, Germany; ³Pharmaceut. and Biomed. Sci., Johannes Gutenberg-University Mainz, Mainz, Germany

Abstract: Mitochondrial dysfunction plays a central role in Alzheimer's disease (AD), with impaired protein import contributing to neurodegeneration. Mitochondria depend on a sophisticated import system involving proteins encoded by both nuclear and mitochondrial deoxyribonucleic acid (DNA). While most mitochondrial proteins are produced in the cytoplasm from nuclear genes, their import into mitochondria requires chaperones like heat shock proteins (Hsps) Hsp70 and Hsp90, along with translocase complexes such as TOM (translocase of the outer membrane) and TIM (translocase of the inner membrane). Impairments in this machinery can result in protein misfolding and aggregation, which are characteristic of neurodegenerative disorders. By integrating proteomics, Western blot, and messenger ribonucleic acid (mRNA) sequencing analyses, we detected notable changes in the import of nuclear-encoded precursor proteins for the mitochondrial respiratory chain. In our AD cell model based on human embryonic kidney (HEK293) cells expressing wild-type amyloid precursor protein (APPwt), we observed dysregulated expression of Hsp90 and Hsp70, along with altered TOM complex subunits. These alterations were accompanied by mislocalization of mitochondrial precursor proteins, indicating defects in protein targeting and translocation. Supporting these findings, mRNA sequencing data from the ROSMAP (Religious Orders Study and Memory and Aging Project) study showed similar dysregulation of the mitochondrial import machinery. Key chaperones, including Hsp90 and Hsp70, and subunits of the TIM and TOM complexes displayed aberrant expression patterns. Notably, we identified sex-specific differences in the expression of these components, suggesting that mitochondrial protein import may be differentially regulated in males and females. Together, our findings highlight the central role of mitochondrial protein import in the pathophysiology of Alzheimer's disease. Disruptions in protein targeting and translocation may represent an underrecognized mechanism contributing to neurodegeneration, potentially shaped by sex-dependent factors. Targeting these offers promising therapeutic avenues for addressing mitochondrial dysfunction in Alzheimer's and related neurodegenerative disorders.

Disclosures: J. Brechtel: None. M. Joerg: None. K. Friedland: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.12/E1

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Research Foundation of Korea (NRF) Grant
2023R1A2C1004955

Title: Amyloid beta oligomer triggered endoplasmic reticulum stress and apoptosis are suppressed by Mitofusin 1 and 2 overexpression in N2a APP^{swe} cells

Authors: *J. LEE^{1,2}, D. LEE^{1,2};

²Sch. of Life Sciences, BK21 FOUR KNU Creative BioResearch Group, ¹Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder, with amyloid beta oligomers (A β O) as toxic pathological markers. A β O disrupt mitochondrial function and reduce mitochondrial fusion. While mitofusin (Mfn) 1 and Mfn2 are key mitochondrial fusion proteins, Mfn2 also supports endoplasmic reticulum (ER) function due to its ER localization. Previous studies suggest A β O exacerbates ER stress, though the mechanisms are unclear. In this study, we used N2a APP^{swe} cells (mouse neuroblastoma cells overexpressing the Swedish-mutated amyloid precursor protein) to explore Mfn's role in ER stress. We found that A β increased cellular toxicity, ER stress markers, and ER expansion in N2a APP^{swe} cells. Overexpression of Mfn1 and Mfn2 mitigated A β O-induced ER stress and decreased apoptosis in these cells. In conclusion, our findings suggest that Mfn1 and Mfn2 reduce ER stress and apoptosis, laying a foundation for future research into their roles in A β O-mediated ER stress and AD pathogenesis.

Disclosures: J. Lee: None. D. Lee: None.

Poster

PSTR014: Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR014.13/E2

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

Support: Fondo Italiano per la Scienza (FIS) MUR24MDILU_01

Title: Uncovering a novel role for cap2 in the regulation of mitochondrial dynamics in neurons

Authors: *R. STRINGHI¹, C. MACCHI¹, M. RUSCICA¹, M. B. RUST^{2,3}, C. W. CULMSEE⁴, D. MAUCERI^{6,5}, M. DILUCA¹, S. PELUCCHI¹, E. MARCELLO¹;

¹Dept. of Pharmacol. and Biomolecular Sci. "Rodolfo Paoletti", Univ. of Milan, Milano, Italy;

²Mol. Neurobio. Group, Inst. of Physiological Chem., Philipps-University of Marburg, Marburg,

Germany; ³Ctr. for Mind, Brain and Behavior (CMBB), Univ. of Marburg and Justus-Liebig-University Giessen, Marburg, Germany; ⁴Inst. for Pharmacol. and Clin. Pharm., ⁵Dept. Mol. and Cell. Neuroscience, Inst. of Anat. and Cell Biol., Univ. of Marburg, Marburg, Germany; ⁶Dept. of Neurobiology, Interdisciplinary Ctr. for Neurosciences (IZN), Univ. of Heidelberg, Heidelberg, Germany

Abstract: Mitochondrial plasticity is the ability of these organelles to adapt their morphology, position, and function in response to energy demand. This process is essential for neuronal health, supporting synaptic activity, calcium homeostasis, and neurotransmitter synthesis. These events rely on a dynamic balance between mitochondrial fusion and fission, which are tightly regulated by actin polymerization and actin-binding proteins such as cofilin and INF2. Elevated intracellular Ca^{2+} activates INF2, promoting F-actin assembly at endoplasmic reticulum (ER)-mitochondria contact sites, where Drp1 is recruited to initiate fission. Cofilin also regulates fission by modulating Drp1 distribution and activity. Cofilin and INF2 share a common protein partner: cyclase-associated protein 2 (CAP2), a synaptic actin-binding protein implicated in synapse plasticity and Alzheimer's disease (AD) synaptic failure.

Here, we characterized the role of CAP2 in regulating mitochondrial dynamics. In neuronal cultures transduced with a viral vector expressing an shRNA targeting CAP2, we observed alterations in mitochondrial morphology and network. These changes were accompanied by disruptions in mitochondrial dynamics, as demonstrated by fluorescence recovery after photobleaching (FRAP) experiments. CAP2 deletion led to a marked increase in the levels of its protein partners INF2 and cofilin, promoting cofilin activation. These findings suggest a disruption in mitochondrial fission process, as evidenced by reduced Drp1 levels and changes in its phosphorylation status, which are critical for proper fission. In contrast, levels of mitofusins, key regulators of mitochondrial fusion, remained unaffected by CAP2 downregulation. Furthermore, our study provided evidence of a dramatic decrease in the total area covered by the mitochondrial network triggered by the absence of CAP2 due to an impairment of mitobiogenesis pathway.

Overall, these findings disclose a critical role of CAP2 in controlling mitochondria dynamics in neurons. Considering that CAP2 expression is reduced in AD patients, our results provide a potential cellular mechanism implicated in neuronal mitochondria vulnerability in AD.

Disclosures: R. Stringhi: None. C. Macchi: None. M. Ruscica: None. M.B. Rust: None. C.W. Culmsee: None. D. Mauceri: None. M. DiLuca: None. S. Pelucchi: None. E. Marcello: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.01/E3

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

Support: IUSM TREAT-AD Center: Project U54AG065181
IU/JAX/PITT MODEL-AD Center: Project U54AG054345

Title: Pharmacodynamic changes in the SAA mouse model following PLC γ 2 targeted small molecule treatment

Authors: *L. E. ROSKAM¹, B. CLAYTON², L. M. BEDFORD⁵, S. J. BISSEL³, H. HUHE⁶, S.-P. WILLIAMS⁸, E. MASON⁹, S. CHU⁴, B. T. LAMB¹⁰, T. I. RICHARDSON¹¹, S. J. SUKOFF RIZZO⁷, J. L. DAGE¹²;

¹Neurol., ²Dept. of Clin. Pharmacol., ³Stark Neurosciences Res. Inst., ⁴Clin. Pharmacol., Indiana Univ. Sch. of Med., Indianapolis, IN; ⁵Med. and Mol. Genet., IU Sch. of Med., Indianapolis, IN; ⁶Dept. of medicine, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; ⁷Dept. of Med., Univ. of Pittsburgh Sch. of Med., PITTSBURGH, PA; ⁸Aging Inst., Univ. of Pittsburgh, Pittsburgh, PA; ⁹Pharmacol. and Toxicology, Indiana Univ., Indianapolis, IN; ¹⁰Med. and Mol. Genet., Stark Neurosciences Res. Inst., Indianapolis, IN; ¹¹Med., Home, Indianapolis, IN; ¹²Neurol., Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Phospholipase C gamma 2 (PLC γ 2) is an essential signaling molecule expressed peripherally in leukocytes in the central nervous system (CNS) by microglial cells. In recent studies, a genetic variant, PLCG2^{P522R}, was found to be protective against Alzheimer's Disease (AD), suggesting that the modulation of PLC γ 2 may alter disease progression through effects on neuroinflammation and microglial function. This study aims to investigate the pharmacodynamic (PD) impact of PLC γ 2 targeted small molecule TAD-0411060 on neuroinflammatory responses in the hAPP-SAA mouse model by profiling protein expression in plasma and brain lysates utilizing the ALAMAR Biosciences Nucleic acid Linked Immuno-Sandwich Assay (NULISA). Aged male and female hAPP-SAA (JAX# 034711; aged 15-18 months) were treated with the IUSM TREAT-AD Center compound TAD-0411060 (100 mg/kg or vehicle, PO) BID (200 mg/kg/day) for 13 or QID (100 mg/kg/day) for 28 days. hAPP-WT littermate controls were aged and treated with vehicle as a control for the disease model. Following chronic treatment, brain and EDTA plasma were collected for PD analyses. Samples were processed and analyzed on the ARGOTM HT platform using the NULISAseqTM Mouse Panel 120. Biomarker detectability was high overall, with 95.7% detected in plasma and 71.3% in brain lysates, representing biomarkers exceeding the lower limit of detection (LOD). In both plasma cohorts, TAD-0411060 resulted in increased plasma levels of erythropoietin (EPO), α Synuclein (snca), phosphorylated α Synuclein 129 (pSnca129) and IL1RL1 for SAA mice. Differentially expressed proteins (fold change $\pm$ 1, p < 0.05) were identified in the high dose cohort. Upregulated proteins in plasma in response to TAD-0411060 treatment included pSnca.129, snca, EPO, ENO2, and Igmn; Cxcl5 was found to be downregulated. In plasma from the low dose cohort, EPO and pSnca129 remained elevated, with no significant downregulation. For brain lysates, PRL was upregulated in response to treatment in the high dose cohort; no changes were observed in the low dose cohort. These findings suggest that TAD-0411060 influences multiple pathways relevant to neurodegeneration, specifically those involving inflammatory signaling. Given its emerging role in regulating innate immune responses, targeting PLC γ 2 represents a promising pharmacological therapeutic strategy in AD. The biomarker panel employed in this model provided a quantitative assessment of 120 proteins from plasma and allowed the assessment of AD related biomarkers in parallel in a small volume of sample.

Disclosures: L.E. Roskam: A. Employment/Salary (full or part-time): Indiana University School of Medicine. Other; No financial support received; Alamar Biosciences has expressed potential interest in supporting conference travel. B. Clayton: A. Employment/Salary (full or

part-time): Indiana University School of Medicine. **L.M. Bedford:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **S.J. Bissel:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **H. Huhe:** A. Employment/Salary (full or part-time): University of Pittsburgh School of Medicine. **S. Williams:** A. Employment/Salary (full or part-time): University of Pittsburgh School of Medicine. **E. Mason:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **S. Chu:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **B.T. Lamb:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **T.I. Richardson:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **S.J. Sukoff Rizzo:** A. Employment/Salary (full or part-time): University of Pittsburgh School of Medicine. **J.L. Dage:** A. Employment/Salary (full or part-time): Indiana University School of Medicine.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.02/E4

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

Support: Lilly Research Award Program

Title: Discovery of novel biomarker candidates for peripheral forms of alpha-synuclein and their relation to Lewy body pathology

Authors: ***J. HENSEL**¹, **N. PROCTOR**⁴, **K. RUSS**², **B. MA**⁵, **T. A. DAY**⁴, **D. DRIVER**⁵, **J. DAGE**³;

²Med. and Mol. Genet., ³Neurol., ¹Indiana Univ. Sch. of Med., Indianapolis, IN; ⁴Eli Lilly and Co., Indianapolis, IN; ⁵Eli Lilly and Co., San Diego, CA

Abstract: Alpha-synuclein (aSyn) is a pre-synaptic protein abundant throughout the central nervous system (CNS). Aggregation of aSyn into intraneuronal protein aggregates, called Lewy bodies, is the pathological hallmark of neurodegenerative disorders called synucleinopathies, which includes Parkinson's disease (PD) and dementia with Lewy bodies (DLB). The current gold-standard for antemortem diagnosis of Lewy body pathology is the cerebrospinal fluid (CSF) real-time quaking induced conversion (RT-QuIC) assay. However, to date, this approach has been unsuccessful in blood due to lack of sensitivity for forms specific to Lewy bodies. A major drawback of the RT-QuIC assay is that it is bimodal and not quantitative. The aim of this study is to discover a quantitative blood-based biomarker assay specific for Lewy body diseases. We developed 16 in-house aSyn antibodies with 14 targeting the C-terminal region, one targeting the N-terminus, and one targeting the pathological modification at Serine 129 (pS129). We used immunoprecipitation (IP) followed by Western blotting (IP-WB) and biolayer interferometry binding characterization to select the top antibody candidates. Plasma samples from 25 control and 25 PD patients were obtained from the IU Neurology Biorepository. These samples were

analyzed by IP using the top antibody biomarker candidates. This IP product will be analyzed by mass spectrometry (IP-MS) and by the RT-QuIC assay (IP-SAA). These same 50 plasma samples were also analyzed using an in-house ELISA assay with antibodies specific for pS129 and total aSyn. Out of 16 aSyn targeting antibodies, we identified 7 as the top antibody biomarker candidates. Using the Tecan Fluent, we will perform IP-MS and IP-SAA on our 25 healthy control and 25 PD plasma samples. From our IP-MS analysis, we expect to find a proteomic profile specific to Lewy body pathology that can then be leveraged as a biomarker signature. The results from plasma IP-SAA are expected to successfully distinguish healthy control from PD and would be the first blood-based assay capable of detecting Lewy body pathology. We developed a biosensor cell line using HEK293T cells overexpressing human A53T-aSyn fused to mVenus (aSyn-mVenus). To confirm the pathological nature of the IP-SAA product, we will treat the HEK-aSyn-mVenus biosensor cell line with the IP-SAA product and examine the seeding capacity and formation of pathological pS129-aSyn. The discovery of blood-based biomarkers for Lewy body pathology will aid in diagnosis and clinical trial enrollment as well as therapeutic monitoring once disease modifying treatments are advanced to the clinic.

Disclosures: **J. Hensel:** A. Employment/Salary (full or part-time): Indiana University School of Medicine. **N. Proctor:** A. Employment/Salary (full or part-time): Eli Lilly and Co.. **K. Russ:** None. **B. Ma:** A. Employment/Salary (full or part-time): Eli Lilly and Co. **T.A. Day:** A. Employment/Salary (full or part-time): Eli Lilly and Co. **D. Driver:** A. Employment/Salary (full or part-time): Eli Lilly and Co. **J. Dage:** A. Employment/Salary (full or part-time): Indiana University School of Medicine, Monument Biosciences.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.03/E5

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

Support: Purdue Institute for Integrative Neuroscience pilot grant

Title: Impaired visual discrimination learning and altered oscillations in the primary visual cortex of 5xFAD mouse model of Alzheimer's Disease

Authors: ***M. YIN**¹, V. SALDARRIAGA², K. R. CRAGG¹, A. A. CHUBYKIN²;

¹Weldon Sch. of Biomed. Engin., ²Biol. Sci., Purdue Univ., West Lafayette, IN

Abstract: Working memory is an aspect of human memory that underpins cognitive activities ranging from attention allocation to specific stimuli to complex decision-making. Impairments of working memory are widely observed in progressive neurodegenerative diseases such as Alzheimer's disease (AD). Previous studies have shown that neuronal loss and amyloid- β in AD strongly correlate with cognitive decline. The visual familiarity-evoked theta oscillations (4-8

Hz) present in the primary visual cortex (V1) and higher visual areas have been shown to be characteristic of visual memory encoding. However, the visual familiarity-evoked theta oscillation properties of AD remain elusive. To investigate this, we trained 9-month-old 5xFAD female mice and wild-type (WT) control female mice with a head-fixed discrimination behavior task and conducted extracellular electrophysiological recordings in V1 and the hippocampus simultaneously. AD mice exhibited excessive activity during the task and had a poorer ability to distinguish different stimuli. Local field potentials (LFPs) in V1 show that visual familiarity-evoked theta oscillations in AD have an attenuated duration and higher base frequency compared to WT. The rate and timing of neuronal spike discharges in relation to different visual stimuli also suggest changes in oscillatory properties in AD. Consistent with many EEG research findings on AD, we see altered theta-gamma coupling, where the phase of theta oscillations modulates the amplitude of high-frequency gamma oscillations (30-80 Hz), in AD. Additionally, seizures are frequently observed in AD during the behavior task. High-frequency oscillations (80-250 Hz) as biomarkers of epileptic seizures were detected not only in the hippocampus but also in V1. Overall, this study offers a new perspective for understanding working memory deficits and shaping future research directions for Alzheimer's disease.

Disclosures: M. Yin: None. V. Saldarriaga: None. K.R. Cragg: None. A.A. Chubykin: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.04/E6

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

Support: NIH Grant R01 AG071228-01A1

Title: Exosome profiling of aging and Alzheimer's disease using a novel protocol for exosome isolation from mouse brain tissue

Authors: *C. C. H. BARKER¹, S. M. JAKES¹, D. A. LINSEMAN²;

¹Biol. Sci., ²Biol., Univ. of Denver, Denver, CO

Abstract: Alzheimer's disease (AD) is considered the most common neurodegenerative disease worldwide, yet the accuracy of assessing the progression of neuropathology and neuroinflammation in patients is limited. Diagnostic tests for AD consist of cognitive assessments, neurological tests, and amyloid-PET scans, all of which may not give clinicians an accurate and precise picture of the neuropathology of the patient. Recent research on blood exosome biomarkers of AD has focused on developing a minimally invasive diagnostic test. However, before blood biomarkers can be used in clinical settings, research on their validity and association with brain pathology needs to be conducted. The goal of this project is to develop a novel method for isolating neuron-derived, astrocyte-derived, and microglia-derived small extracellular vesicles (sEVs) from brain tissue; then, investigate the cargo of these sEVs and

compare between young vs old and 3xTg-AD vs wild-type (WT) mice to identify biomarkers of aging and Alzheimer's disease. We will then compare the protein cargo of exosomes isolated from brain tissue and plasma of the same mouse groups to discern if the biochemistry of both sEV populations is significantly correlated. The protocol developed in this project for obtaining sEVs from brain tissue uses immunoaffinity capture techniques to specifically isolate sub-populations of exosomes; using streptavidin-coated magnetic beads and a sequential isolation method ensures a higher level of purity, while keeping time and costs down. Methods used to validate this protocol include transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA), dot blots, and western blots. We currently are isolating brain-derived sEVs from brain tissue of 4 mouse groups (n = 24 each): 4-month-old 3xTg-AD, 20-month-old 3xTg-AD, 4-month-old WT, and 20-month-old WT. The results of this ongoing study have demonstrated the enrichment of neuron-derived sEVs (NDEVs) and astrocyte-derived sEVs (ADEVs) with the correct size and morphology of exosomes in samples isolated from brain tissue using our protocol. Future directions for this study will involve measuring AD-specific biomarkers in the acquired exosome samples and comparing biomarker results of young/old and 3xTg-AD/WT mouse groups. We will investigate various biomarkers of neuroinflammation and neuronal injury, such as: A β 40, A β 42, neurofilament light chain (NfL), Tau, p-Tau, GFAP, Vimentin, S100 β , IL-6, TNF- α , IL-1 β , and IL-10. Conclusions from this study will advance research on Alzheimer's disease biomarkers for diagnosis and prognosis, as well as introduce new techniques for exosome isolation from tissue.

Disclosures: C.C.H. Barker: None. S.M. Jaques: None. D.A. Linseman: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.05/E7

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

Support: NIH Grant R01-NS033310
NIH Grant U54-NS100064
NIH Grant 1R16-NS131108
NIH Grant R01AG066212
VA Merit 1 I01 BX005919-01
VA Merit BX004332-01

Title: Disruption of Electrophysiological Rhythms and Memory Impairment in an Alzheimer's Transgenic Rat Model

Authors: X. TAO¹, U. DEVARAJ², M. WANG¹, C. ZHU³, A. BRAGIN³, G. M. COLE⁵, J. ENGEL, Jr.⁶, S. A. FRAUTSCHY⁷, *L. LI^{1,4};

¹Univ. of North Texas, Denton, TX; ²Dept. of Neurol., David Geffen Sch. of Med. at UCLA, Los Angeles, CA; ⁴Neurol., ³Univ. of California Los Angeles, Los Angeles, CA; ⁵Neurol. and Med.,

UCLA/ GLAVA GRECC, Los Angeles, CA; ⁶Neurobiology, and Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; ⁷Neurol., UCLA and VA, Los Angeles, CA

Abstract: Alzheimer's disease (AD) are the most prevalent causes of dementia, characterized by progressive memory loss and cognitive decline. Abnormal electrophysiological patterns, especially the interictal epileptiform discharges (IEDs) and high-frequency oscillations (HFO) have been observed in the mice AD model and suggested to contribute to cognitive dysfunction. However, comprehensive evaluations of IEDs, including across different brain regions remain limited, and their impact on cognitive performance and neuropathology is unclear, particularly in AD models with greater cognitive complexity than mice and comorbidities that may increase vulnerability. Our goal is to fill this knowledge gap of understanding how IEDs and HFOs contribute to cognitive decline and neuropathology in AD, which will potentially advance the field with new biomarkers to predict dementia in the prodromal period. We investigate these effects in an AD (PS1/APP) rat model (FAD+) with coexisting hypertension-associated small vessel disease (SVD), as well as in their transgene-negative littermates (FAD-). We conducted behavioral experiments at month 6, 8 and 11 of animal age, alongside the neural signal recording at month 8 and 11. AD pathology (neuritic plaques and hyperphosphorylated tau) and novel biomarkers (14-3-3) or biomarkers common to both disorders (neuropeptide Y, astrocyte and microglia) were evaluated at the end of the experiment. Seizures were observed in three out of 14 FAD+ rats. Results showed that the IEDs were significantly greater in the FAD+ rats compared to the FAD- at all tested periods, correlating with the development of changes in neuropathological biomarkers. Furthermore, the coupling strength between IEDs and HFOs was significantly elevated in FAD+ rats, especially during the later stages of disease progression. In addition FAD+ rats exhibited similar deficits in both learning and recall ability in both age cohorts, which correlated best with increased IED-HFO coupling strength. However, no correlation was observed in the FAD- group. Our findings suggest that the pathological synchronization between IEDs and HFOs in the hippocampus, along with neuropathological changes in both the hippocampus and entorhinal cortex may contribute to memory dysfunction in AD, highlighting a potential mechanistic link between epileptiform activity with epilepsy and AD biomarker changes and cognitive decline.

Disclosures: X. Tao: None. U. Devaraj: None. M. Wang: None. C. Zhu: None. A. Bragin: None. G.M. Cole: None. J. Engel: None. S.A. Frautschy: None. L. Li: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.06/E8

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

Support: Reynolds Fund, Oregon State University Foundation

Title: Early sleep fragmentation in heterozygous 5xFAD mice is predominantly driven by females

Authors: *K. J. KIM¹, A.-R. L. VILLEGAS², A. KELLEY³, T. M. HAGEN¹, H. KLOEFKORN⁴, K. R. MAGNUSSON⁵;

¹Linus Pauling Inst., ²Chemical, Biological, and Environmental Engin., ³Dept. of Biochem. & Biophysics; Linus Pauling Inst., ⁴Chemical, Biological, and Environ. Engin., ⁵Dept Biomed Sci, Coll Vet Med. & Linus Pauling Inst., Oregon State Univ., Corvallis, OR

Abstract: Alzheimer's disease (AD) is an incurable brain disease that is the most common form of dementia. There is a critical need to design interventions into early events to prevent or delay the onset of the disease. Sleep alterations have long been associated with Alzheimer's disease (AD), but whether it is an early symptom or only develops later in the pathological progression remains unknown. The 5xFAD mouse model has five mutations, linked to familial (inherited) AD, which leads to amyloid overexpression. Intraneuronal amyloid beta protein is present by 1 month of age, but plaques do not form until 2-4 months old. Based on early mitochondrial and electrophysiology changes, we hypothesized that 5xFAD heterozygotes (HET) would show non-invasive behavioral alterations early in development. 5xFAD heterozygous (Het) mice and wild-type (WT) littermates at 1, 2, 3, 4 and 6 months of age (n=5-7) were measured via previously validated non-invasive sensors for 12 hours (6pm-6am) to score 3-stage sleep/wake: wake, non-rapid eye movement sleep (NREM), and REM sleep. During sleep recordings, mice were pair-housed by sex in home cages with a temporary insert enabling sight, smell, and sound interactions. Sleep was scored manually in 10-second epochs in Spike2 (Cambridge Electronic Design, Inc.). A custom MATLAB script calculated these sleep measures: percentage times spent asleep or in REM sleep, sleep fragmentation index (SFI), microarousal index, REM and NREM sleep bout durations, and REM sleep onset latency. ANOVAs were performed between genotypes, sex and age. Alterations in sleep architecture were identified in Het animals as early as 1 month of age. Compared to WT littermates, Het mice exhibited increased sleep fragmentation and more microarousals. These effects were more pronounced in females than in males. Across ages, Het mice showed increased time awake and decreased sleep time, latency to rapid eye movement (REM) and total time in REM, although percent time spent in REM did not differ significantly from WT controls. Most genotype differences widened by 6 months of age. Female mice specifically exhibited higher microarousal index and percent time in wake and shorter latency to REM relative to males. Given that transgene expression in a separate set of mice was evidenced by day 15 in 5xFAD Hets and escalated with age, the observed sleep dysregulation is likely reflective of the accumulation of soluble amyloid-beta oligomers. These results highlight early, sex-specific disruptions in sleep that may serve as preclinical markers of AD-related pathology.

Disclosures: K.J. Kim: None. A.L. Villegas: None. A. Kelley: None. T.M. Hagen: None. H. Kloefkorn: None. K.R. Magnusson: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.07/E9

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

Support: Alzheimer's Association SAGA grant

Title: Molecular signatures of sex biased cognitive trajectories in aged marmosets preliminary findings

Authors: *A. BHARADWAJ¹, J. N. RAUCH², A. LACREUSE³, S. L. PADILLA⁴;

¹Neurosci. and Behavior, ³Psychological and Brain Sci., ²Univ. of Massachusetts Amherst, Amherst, MA; ⁴Univ. of Massachusetts, Northampton, MA.

Abstract: Women account for nearly 2/3rd of Alzheimer's disease (AD) cases in the U.S., and the manifestation and progression of the disease exhibit marked sex differences. However, the biological mechanisms driving these disparities remain largely unknown. Gaining insight into sex-specific vulnerability is essential for developing targeted and effective therapeutic strategies. Current evidence suggests that hormonal, genetic, neural, and lifestyle factors interact to shape differential risk. One key hormonal factor is the drop in estrogen levels during menopause, which is associated with increased neuroinflammation, reduced neuroprotection, and alterations in brain function, potentially heightening the risk of neurodegeneration in aging women. The common marmoset is a short-lived nonhuman primate with strong potential for aging and neurodegenerative research. Prior studies have shown that female marmosets undergo earlier and more rapid cognitive decline than males, despite showing similar behavioral profiles. Interestingly, this difference was not linked to disparities in classical neuropathology, such as β -amyloid accumulation or glial cell density in the hippocampus (HPC) or dorsolateral prefrontal cortex (dlPFC), suggesting alternative molecular contributors. In this exploratory study, we use RNAscope in situ hybridization to investigate sex-based differences in the expression of aromatase and hormone receptors across three key brain regions: dlPFC, hypothalamus, and HPC. Recent studies have identified phosphorylated tau in marmoset brain tissue. We will investigate the impact of sex and age on tau pathology in the context of cognitive decline. We will assess a panel of phosphorylated tau epitopes representing multiple stages of AD pathology using immunofluorescence (IF) across brain regions. Ideally, we will combine tau IF with RNAscope expression data to elucidate a more comprehensive view of sex- and age-specific neurodegenerative trajectories. To our knowledge, this combined histological and pathological approach has not yet been applied in the marmoset model. We are analyzing right hemisphere brain tissue from 17 aged marmosets (9 males, 8 females, ages 7.7-10.3 years) that have undergone long-term cognitive assessments. RNAscope HiPlex v2 (Bio-Techne) enables multiplexed labeling of up to 8 transcripts using sequential hybridization, fluorophore tagging (Alexa Fluor 488/750, Dylight 550/650), and DAPI for probe alignment. Initial findings in three animals confirm target detection sensitivity. IF using PHF-tau antibody has also verified the presence of tau pathology. Further analysis across the full cohort is underway.

Disclosures: A. Bharadwaj: None. J.N. Rauch: None. A. Lacreuse: None. S.L. Padilla: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.08/E10

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

Support: NIH Grant R00DC018600

Title: Establishing a Gerbil Model to Study the Interaction Between Hearing Loss and Alzheimer's Disease Pathology

Authors: *M. CALVANO¹, K. M. BIESZCZAD², J. YAO³;

¹Rutgers Univ., New Brunswick, NJ; ²Psychology, Behavioral and Systems Neurosci.,

³Otolaryngology, Rutgers Univ., Piscataway, NJ

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder marked by the accumulation of amyloid-beta (A β) oligomers and hyperphosphorylated tau tangles. Epidemiological studies consistently link hearing loss to increased AD risk and accelerated cognitive decline, yet the underlying mechanisms remain poorly understood. Here, we investigate how hearing loss influences AD-related pathology using a gerbil model. Gerbils are well-suited for this work due to their human-like hearing range and natural production of A β . Unlike other rodent models, gerbils express A β 40 and A β 42 sequences identical to the human isoforms at key amino acid residues, enabling human-like aggregation and toxicity. To model AD pathology, we oligomerized human A β 1-42 and injected it into the lateral ventricle of adult gerbils. After a 4-week recovery period, brains were processed and analyzed via immunofluorescence. We quantified mean fluorescence intensity (MFI) of A β (6E10) and phosphorylated tau (p-Tau, AT8) in the hippocampus (HPC), auditory cortex (AC), and parietal cortex (PC). Comparisons were made across groups of normal-hearing controls versus animals injected with A β , and normal-hearing controls versus animals with noise-induced hearing loss (NIHL). Our preliminary findings reveal distinct regional effects. A β -injected animals exhibited significantly elevated levels of 6E10 expression in all regions compared to controls (HPC: $p < 0.05$, AC: $p < 0.05$, and PC: $p < 0.01$). p-Tau expression was elevated in PC ($p < 0.05$) but not in HPC or AC. In NIHL animals, compared to controls, 6E10 expression was significantly higher in AC ($p < 0.05$) and PC ($p < 0.005$), but not in HPC. Furthermore, p-Tau levels were elevated across all regions in NIHL compared to controls (HPC: $p < 0.005$, AC: $p < 0.0005$, and PC: $p < 0.0001$). The region-specific effects of NIHL on A β and p-Tau accumulation, particularly the pronounced increase in p-Tau in auditory-related regions, suggest that chronic sensory deprivation may exacerbate AD pathology in a region-specific manner. These findings indicate that hearing loss amplifies AD-related pathology, especially in cortical regions involved in auditory and cognitive processing (AC and PC). Thus, gerbil represents a valuable model for investigating the mechanistic link between sensory loss and AD progression.

Disclosures: M. Calvano: None. K.M. Bieszczad: None. J. Yao: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.09/E11

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

Support: NIH grants EY031697 (WKJ)
P30 EY022589 (Vision Research Core Grant)

Title: Early Retinal Mitochondrial Dysfunction in a Mouse Model of Alzheimer's Disease

Authors: *Z. SHEN¹, T. BASTOLA², K.-Y. KIM³, M. POUDEL⁴, W. JU⁵;

¹Ophthalmology, Univ. of California San Diego, San Diego, CA; ²Univ. of California San Diego, SAN DIEGO, CA; ³Natl. Ctr. Microscopy and Imaging, Univ. of California San Diego, La Jolla, CA; ⁴Univ. of California San Diego, San Diego, CA; ⁵Ophthalmology, Univ. of California San Diego, La Jolla, CA

Abstract: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder marked by progressive cognitive decline. Increasing evidence suggests that AD pathology extends beyond the brain, implicating peripheral tissues such as the retina in the disease process. To investigate early molecular changes in the retina, we examined mitochondrial dynamics and bioenergetics in 3-month-old female PSAPP mice, a well-established transgenic model of AD, and age-matched wild-type (WT) controls. Our analyses revealed significant dysregulation of mitochondrial dynamics in PSAPP retinas. Specifically, we observed decreased expression of A-kinase anchoring protein 1 (AKAP1) and reduced phosphorylation of dynamin-related protein 1 (Drp1) at Ser637, alongside elevated total Drp1, indicating a shift toward mitochondrial fission. Fusion-related proteins optic atrophy 1 (OPA1) and MFN1/2 were also diminished, suggesting an imbalance in fission-fusion homeostasis. Further, impaired mitochondrial respiration was evidenced by alterations in oxidative phosphorylation (OXPHOS) profiles and reduced expression of mitochondrial biogenesis regulators TFAM and PGC-1 α . Decreased AMP-activated protein kinase (AMPK) phosphorylation indicated compromised energy homeostasis. In parallel, upregulation of pro-apoptotic marker active BAX, stress kinase p38, and mitophagy-associated proteins LC3B and p62 pointed to elevated cellular stress and defective mitochondrial quality control. These findings highlight early retinal mitochondrial dysfunction as a hallmark of AD pathology in PSAPP mice and suggest the potential utility of retinal biomarkers for early AD detection and monitoring.

Disclosures: Z. Shen: None. T. Bastola: None. K. Kim: None. M. Poudel: None. W. Ju: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.10/E12

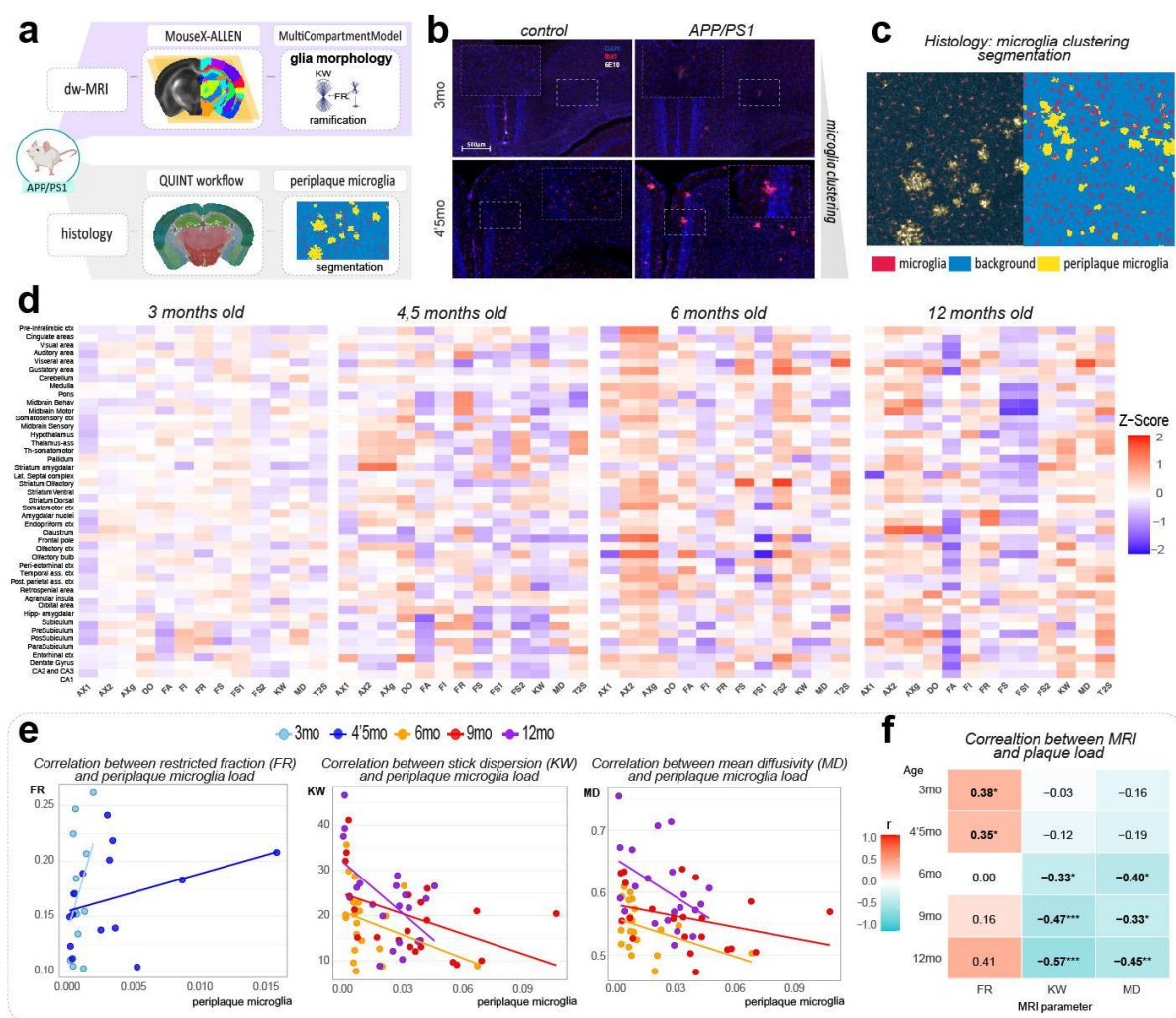
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SDS_GENT_2022 | CIDEAGENT
SDS-FPM | Fundación Maragall

Title: Dissecting the association between MRI microstructural early alterations and plaque-associated microglia reactivity in Alzheimer's disease mouse model

Authors: *P. MARTÍNEZ TAZO, A. CERDÁN CERDÁ, E. SAXTON, A. S. MAROTO, J. SANCHEZ MUT, S. DE SANTIS;
Inst. of Neurosci. of Alicante-UMH-CSIC, Alicante, Spain

Abstract: INTRODUCTION: Microstructural damage in Alzheimer's disease begins years before cognitive symptoms appear [1]. Non-invasive tools to detect early Alzheimer-specific patterns, like early neuroinflammation that later turns chronic, are urgently needed. Advanced diffusion-weighted (dw) MRI biomarkers capturing microglia morphology changes have become available [2], making inflammation a potential early target. Here, we tested the association between dwMRI inflammation markers and glia changes over time in APP/PS1 mice and controls. METHODS: APP/PS1 mice and controls (15/20, 50%f) were scanned at 3, 4.5, 6, 9, and 12 months (7T Bruker). Conventional and advanced dwMRI were used to extract DTI markers (MD) and inflammation-sensitive metrics (FR, KW). MRI parcellation used the MouseX-DW-ALLEN Atlas [3]. A subset (4/4) was perfused and stained for plaques (6E10), nuclei (DAPI) and microglia (Iba-1), segmented with QUINT [4] (Figure1a). Z-score highlighted regions and MRI markers discriminating groups. Pearson correlation assessed MRI-histology associations at each stage. RESULTS AND DISCUSSION: Histology showed early amyloid deposition and periplaque microglia in APP/PS1 (Figure1b) and allowed segmenting clustered microglia (Figure1c). MRI revealed sensitivity to group differences starting at 3 months and increasing in time (Figure1d). Correlation between histology and MRI revealed stage-specific associations (Figure 1e-f). Process dispersion (KW) and mean diffusivity (MD) showed progressively stronger negative correlations with microglia at mid (6) and late (9-12) stages, reflecting progressive pathology (*p < 0.05, **p < 0.01, ***p < 0.001). Interestingly, at early stages (3-4.5), restricted fraction (FR) showed a positive correlation, suggesting increased diffusion restriction near early deposits. These preliminary results point at FR as a non-invasive marker sensitive to early-stage Alzheimer-specific microstructure..



[1] Sochocka, 2019. [2] Garcia-Hernandez, 2022.
 [3] Martínez-Tazo, 2024.
 [4] Yates, 2019.

Disclosures: P. Martínez Tazo: None. A. Cerdán Cerdá: None. E. Saxton: None. A. S. Maroto: None. J. Sanchez Mut: None. S. De Santis: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.11/E13

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

Support: NIH Grant
Riney Foundation Grant

Title: Identification of Key Molecules in the Brain of PSEN1 Pig Models Developed to Help Study Alzheimer's Disease

Authors: *E. KIESEWETTER¹, K. RODRIGUEZ-LUKEY², S. JEON³, T. J. JAROME⁴, T. A. ALLEN⁵, K. LEE³;

¹Animal Sci., ²Advance Light Microscopy Core, ³Univ. of Missouri, Columbia, MO; ⁴Virginia Tech., Blacksburg, VA; ⁵Psychology, Florida Intl. Univ., Miami, FL

Abstract: Previously, a clinically relevant swine model (*PSEN1*^{ΔE9/+}) to study early onset Alzheimer's Disease (AD) has been established by utilizing genome editing system. Cognitive assessment and MRI scans of their brain indicate that these pigs carry cognitive deficiencies and abnormal brain physiology, respectively, demonstrating their relevance to study AD. This study was conducted to characterize cell morphology and distributions in the brain cortex of *PSEN1*^{ΔE9/+} and wildtype (WT) pigs at 12-14 months of age. First, we quantified the level of Amyloid beta (Aβ) and Tau protein (Tau) in their brain using western blotting. There were no quantitative differences between Aβ and Tau concentrations in *PSEN1* and WT pigs (n=3 per model). Next, we examined if the localization of Aβ and Tau protein in the brain cortex were different between *PSEN1* and WT pigs. Brains from *PSEN1* and WT pigs (12-14 months old) were collected, fixed, then sectioned in Optimal Cutting Temperature blocks at 20 μm thickness. The brain's mid cortex was selected as it provides a good generalization of the entire brain. Immunofluorescent staining was performed to identify Amyloid-beta protein plaques (Aβ), Tau protein (Tau), reactive microglia (Iba1), astrocytes (GFAP), neurons (NeuN), and nuclei (DAPI) in age-matched *PSEN1* and WT brains. In the gray matter, there are unusual distributions and accumulation of cells positive for Aβ and Tau in the brain of *PSEN1* pigs compared to WT controls. In the brain of *PSEN1* pigs, the morphology of neurons showed evidence of early Tau pre-tangle formation as well as mature and ghost tangles at a higher frequency than in WT brains. Accumulation of Tau was identified in the neurons that were square shaped, indicating their localization on the dendrites. Additionally, some neurons were misshapen and shrunken due to Tau protein envelopment. In the white matter, WT samples showed consistent and localized staining of neuronal markers, whereas the cells in the brains of *PSEN1* pigs were elongated, indicating abnormal activation of these cells. Additionally, the abundance of reactive microglia was higher in *PSEN1* pigs compared to WT animals. Throughout the brains of *PSEN1* pigs, astrocyte morphology consisted of thick processes and atrophied branches. These histological differences suggest that *PSEN1* mutation may lead to gliosis or pro-inflammatory responses in the brain. More in-depth image analyses are being performed to identify statistical differences. Differences in other brain areas, such as the frontal cortex and hippocampus, will also be investigated. These analyses will further validate AD-like pathologies in the PSEN1 pig model.

Disclosures: E. Kieseewetter: A. Employment/Salary (full or part-time): Division of Animal Sciences, University of Missouri, Columbia, MO, USA. K. Rodriguez-Lukey: A. Employment/Salary (full or part-time): MU Advanced Light Microscopy Imaging Core, University of Missouri, Columbia, Missouri, USA. S. Jeon: A. Employment/Salary (full or part-time): Division of Animal Sciences, University of Missouri, Columbia, MO, USA. T.J. Jarome: A. Employment/Salary (full or part-time): School of Animal Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA. T.A. Allen: A. Employment/Salary (full or

part-time): Cognitive Neuroscience Program, Department of Psychology, Florida international University, Miami, FL, USA. **K. Lee:** A. Employment/Salary (full or part-time): Division of Animal Sciences, University of Missouri, Columbia, Missouri, USA.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.12/E14

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

Support: 5R01AG072727-03
UND School of Medicine and Health Sciences

Title: Saliva cytokine concentrations as potential biomarkers of Alzheimer's disease

Authors: ***A. M. FLODEN**¹, C. K. COMBS²;

¹Biomed. Sci., Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND; ²Biomed. Sci., Univ. of North Dakota Sch. of Med., Grand Forks, ND

Abstract: Worldwide approximately 55 million people are living with Alzheimer's disease (AD) and that number is expected to increase to 139 million by 2050. Sensitive and specific biomarkers for identifying early disease are, therefore, attractive to the field. Tau and amyloid beta (A β) protein level changes in both cerebrospinal fluid and plasma have been proposed as indices supporting disease diagnosis. We hypothesized that saliva might also provide a reliable source of biomarkers for assessing disease. Saliva is noninvasive, relatively inexpensive to collect, and contains a multitude of proteins. We have previously quantified elevated A β levels in the saliva of the *App*^{NL-G-F} mouse model of AD. This finding is consistent with some reports of elevated salivary A β in the saliva of AD patients. To characterize additional disease-related protein changes in the saliva, we compared 12-month-old littermate control male and female C57BL/6 wild type and *App*^{NL-G-F} mice using a commercial slide-based cytokine array. There were numerous disease-related changes in cytokine levels. Female *App*^{NL-G-F} mice demonstrated higher levels of IL-1 β , IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17, IL-17F, IL-13, IFN- γ , TGF β 1, IL-21, and IL-22 compared to their wild type female controls. Female *App*^{NL-G-F} mice also had reduced levels of TNFSF11, Osteoactivin, and CRP. Far fewer changes were observed in males. Male *App*^{NL-G-F} mice had elevated levels of Osteoactivin and reduced levels of IL-2 compared to their respective wild type male controls. Based on these robust sex differences in disease levels of cytokines in the mouse model we performed a similar quantitative cytokine analysis from human male and female age-matched healthy control and AD saliva samples. For human male AD saliva, we observed significant elevations in levels of IL-1 α , IL-4, IL-12p70, MMP-13, Osteopontin, and Rank compared to their male control saliva. AD male saliva had reduced levels of MIP-1 α compared to their respective healthy male controls. However, female AD saliva had elevated levels of only IL-1 α compared to their age-matched female controls. These data demonstrate several increases and decreases in saliva cytokine levels as possible biomarkers of

disease in both human and mouse samples. However, understanding the sex and species differences in the specific cytokine changes will require further investigation.

Disclosures: A.M. Floden: None. C.K. Combs: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.13/E15

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

Support: NIH Grant RO1 NS126920

Title: Loss of functional hyperemia and neural dynamics

Authors: *D. AHIRWAR¹, K. XIE², P. J. O'HERRON³;

²Physiol., ¹Augusta university, Augusta, GA; ³Physiol., Augusta Univ., Augusta, GA

Abstract: Functional hyperemia regulates blood flow to activated neurons. Its loss is thought to contribute to neurodegeneration in diseases like Alzheimer's dementia and small vessel diseases. To study the importance of functional hyperemia, we recently developed an optogenetic mouse model to block functional hyperemia by shining light on the brain while activating the cortical tissue with sensory stimulation. Two photon imaging of neuronal Ca²⁺ activity in the visual cortex revealed little change in responses when the hyperemic response was blocked. Here we seek to measure temporally precise neural response properties using electrical recordings. We use a 32-channel flexible multi-electrode array inserted under a glass cranial window to record single-neuron activity and population local-field potentials (LFP). Our preliminary data shows that during the loss of functional hyperemia, LFP amplitude is increased relative to conditions where blood flow is allowed to increase. Individual neuronal units display varying responses. Neurons with high selectivity for the orientation of visual stimuli show a drop-in firing rate along with increased orientation selectivity. Non-selective units display opposite or inconsistent trends. Our control mice with no opsin show no difference in LFP and no trends in single-unit responses. Thus, changes in LFP and single unit dynamics may indicate effects of the loss of functional hyperemia that are not detectable with Ca²⁺ imaging.

Disclosures: D. Ahirwar: None. K. Xie: None. P.J. O'Herron: None.

Poster

PSTR015: Alzheimer's Disease and Related Dementias: Biomarkers: Animal Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR015.14/E16

Topic: I.08. Learning and Memory

Support: PO1AG060882

Title: Effect of human apolipoprotein-E alleles on motor and cognitive function in the Tg-SwDI mouse model

Authors: *R. KASA¹, B. GAMALLO-LANA¹, C. F. LABORC⁴, F. R. GONI⁵, T. M. WISNIEWSKI², A. C. MAR³;

²Neurol., ³Neurosci. and Physiology, Neurosci. Inst., ¹NYU Sch. of Med., New York, NY; ⁴Dept. of Neurosci. and Physiol., New York Univ., New York, NY; ⁵New York Univ. Sch. Med., New York, NY

Abstract: The apolipoprotein-E gene (APOE) is the most significant genetic risk factor for late-onset Alzheimer's disease (AD), with E2, E3 and E4 alleles conferring lower, neutral and higher risk of developing AD. E4 binds to amyloid β (A β) and is strongly associated with increased deposition of amyloid plaques in brain as well as vascular amyloid pathology such as cerebral amyloid angiopathy (CAA). How human APOE interacts with A β and CAA to affect cognitive and behavioral function remains unclear. In this study, we examine how different human APOE isoforms impact cognitive and motor deficits when crossed to a mouse model that mimics human AD and CAA. Targeted replacement human E2, E3 and E4 knock-in C57BL/6J mice were crossed with TgSwDI mice to generate Tg-SwDI/E2, /E3 or /E4 mice homozygous for both human SwDI A β PP and human APOE gene alleles. We analyzed motor (open field, rotarod, grip strength) and cognitive (novel arm location (NAL), Barnes and radial arm mazes) phenotypes across male and female Tg-SwDI, Tg-SwDI/E2, Tg-SwDI/E3, Tg-SwDI/4 and wild type C57BL/6J mice at 13-15-months of age. Tg-SwDI mice had significantly decreased latency to fall in the rotarod and decreased time in the center of the open field relative to wild type controls. Tg-SwDI female mice were hyperactive in the open field relative to wild type females. Tg-SwDI mice also showed significantly reduced novel arm preference/memory in the NAL and found fewer target holes and rewards in the Barnes and radial arm mazes respectively - independent of their motor scores. Tg-SwDI/E4 significantly reduced the hyperactivity of Tg-SwDI females and increased center time in the open field of both sexes. E4 did not significantly alter other Tg-SwDI-associated motor deficits. Unexpectedly, Tg-SwDI/E4 improved NAL novel-arm preference, Barnes and radial arm maze performance relative to Tg-SwDI, and E4-crossed mice were not different from wild type controls. Tg-SwDI/E3 had increased time in center of the open field but did not show any other differences relative to Tg-SwDI animals. Tg-SwDI/E2 did not show significant differences in motor or cognitive performance relative to Tg-SwDI mice. These results indicate that human APOE isoforms differentially modulate the motor and cognitive phenotype of the Tg-SwDI AD/CAA mouse model. Paradoxically, the E4 allele generally resulted in enhanced motor, anxiety and cognitive performance relative to Tg-SwDI mice.

Disclosures: R. Kasa: None. B. Gamallo-Lana: None. C.F. Laborc: None. F.R. Goni: None. T.M. Wisniewski: None. A.C. Mar: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.01/E17

Topic: C.03. Parkinson's Disease

Support: NIH MH113257

Title: Sex-specific neuroinflammation in parkinson's disease, a systematic review of rodent and non-human primate models

Authors: *V. MENDOZA-SILVA¹, C. CANALES¹, Y. RODRIGUEZ ROJAS², D. PEÑA³, K. KURREY¹, F. P. CÁRDENAS², A. DUQUE¹;

¹Neurosci., Yale Univ., New Haven, CT; ²Psychology, Univ. De Los Andes, Bogotá, Colombia;

³Neurosci., Wheaton Col., Norton, MA

Abstract: Sex differences are increasingly recognized as important modulators of Parkinson's disease (PD) pathophysiology, with growing evidence pointing to distinct neuroinflammatory responses in males and females. This systematic review aims to characterize and compare neuroinflammatory profiles in male and female rodents and non-human primates with experimentally induced PD, focusing on validated biomarkers. Following PRISMA 2020 guidelines and registered in PROSPERO (CRD42024600712), we systematically searched PubMed, Scopus, Web of Science, PsycNet, and SciELO for original studies published between January 2014 and May 2025 in English or Spanish. Eligible studies must involve PD induction through neurotoxins, pesticide exposure, or genetic manipulation, report data separately by sex for both experimental and control groups, include at least 3 animals per group, and assess at least one neuroinflammatory marker (e.g., microglial activation, astrocyte markers, cytokines, or mitochondrial dysfunction indicators). Five reviewers will independently assess the risk of bias using SYRCLE's Risk of Bias tool and the ARRIVE guidelines. A structured narrative synthesis will be conducted, given the anticipated heterogeneity across species, induction methods, and measurement techniques. Outcomes will be analyzed separately by sex and marker type, with data extracted from textual and graphical sources using standardized forms and validated through AI assisted tools. Interrater reliability will be monitored using Gwet's AC1, and sensitivity analyses will guide interpretation. Study selection and data extraction are ongoing. This review will provide a critical synthesis of sex related neuroinflammatory dynamics in preclinical models of Parkinson's disease and aims to inform future research on mechanisms and therapeutic targets that differ by sex in neurodegenerative disease.

Disclosures: V. Mendoza-Silva: None. C. Canales: None. Y. Rodriguez Rojas: None. D. Peña: None. K. Kurrey: None. F.P. Cárdenas: None. A. Duque: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.02/E18

Topic: C.03. Parkinson's Disease

Support: NIH MH 113257

Title: Progressive neuromelanin accumulation in normal aging macaques reveals a new signature for selective vulnerability in parkinson's disease

Authors: *C. CANALES¹, J. CHOCARRO², J. L. LANCIEGO², A. DUQUE¹;
¹Yale Univ., New Haven, CT; ²CNS Gene Therapy Program, CIMA - Univ. of Navarra, Pamplona, Spain

Abstract: Recent studies have linked neuromelanin (NM) production over a threshold to the development of Parkinson's disease (PD) neuropathology in animal models. The absence of NM in common laboratory animals such as rodents has hindered the study of its role in PD pathogenesis. NM-levels in non-human primates (NHPs), though lower than in humans, show time-dependent production during normal aging. Understanding the progressive physiological increase of NM will potentially help unveil novel approaches to prevent NM pathological accumulation. Here, a detailed study of the progressive accumulation of NM both in the substantia nigra (SN) and the locus coeruleus (LC) is presented in 7 rhesus macaques spanning from 1 to 26 years old. Both nuclei were identified by staining with neutral red and compared to the same tissue before staining. That is, measurements of the optical density of NM and the occupied intracellular space were performed on unstained tissue to avoid neutral red variable intensity bias. Results show that NM accumulation starts early with undetectable by 1 year and small variable amounts detected by 8 years of age. In one hemisphere of the 8-years old specimen we counted 2,020 and 184 pigmented neurons in the SN and the LC, respectively. This accounts for ~30% of the total pigmented neurons that, per our counts, reach a plateau in both nuclei, in our 11 and 15-years old specimens. In the SN, NM accumulation was considerable in the 3 oldest specimens and accumulation was progressive with the highest accumulation in the oldest. The rate of NM production appeared higher in the dopaminergic (DA) neurons of the SN than in noradrenergic neurons of the LC. Hence, in DA neurons of the SN more intracellular space was occupied by higher levels of NM. Neurons of the SN with optical densities over a set threshold were considered outliers (with high amounts of NM). These neurons may represent a specific vulnerable cell population that needs to be studied. Their distribution along the SN is still being analyzed but are thought to characterize the highly vulnerable ventral tier. Functional impairment due to overproduction of NM is pending to be estimated by analysis of tyrosine hydroxylase staining. Overall, in our small sample, our impression is that although both nuclei start to accumulate NM at the same age and they follow the same pattern of neuronal pigmentation, more NM accumulates within aging DA neurons of the SN than in their noradrenergic neurons of the LC. Outliers were present only in the SN. If the same in humans, this NM profile may underlie DA neuron vulnerability in PD. Materials provided by MacBrain Resource Center.

Disclosures: C. Canales: None. J. Chocarro: None. J.L. Lanciego: None. A. Duque: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.03/

Topic: C.03. Parkinson's Disease

Support: CIHR operating grant
Molson Foundation Neuroengineering Studentship
CIHR-IRTG: CREATE-CITF studentship

Title: Molecular Biomimicry and the Synthetic Synapse: Engineering a stable synaptogenic extracellular matrix

Authors: ***T. A. J. FISHER**¹, A. SHMUEL², T. E. KENNEDY³;
²Neurology, Neurosurgery, Physiology, and Biomed. Engin., ¹McGill Univ., Montreal, QC, Canada; ³Neurol. & Neurosurg., Montreal Neurolog. Institute, Montreal, QC, Canada

Abstract: Synapses are specialized sites of asymmetric cell - cell contact that mediate information transfer between neurons. Surprisingly, synaptic differentiation does not require a cellular target. Hemi-synaptic specializations form quickly at sites of neurite adhesion to microspheres coated with a synaptogenic protein or a synthetic cationic polypeptide like poly-lysine. This raises the possibility that functional hemi-synaptic connections could be directed to form onto engineered surfaces, improving information transfer and biocompatibility. However, studies examining the stability of synaptic specializations formed in brain onto poly-lysine coated beads found they degraded within a few weeks after implantation. Here, we demonstrate that microbeads coated with dendritic polyglycerol amine (dPGA), a non-protein macromolecular biomimetic of poly-lysine, promote enhanced synaptogenesis and synapse stability compared to conventional poly-lysine. We show that dPGA-coated beads cluster neurexin, which is sufficient to direct presynaptic terminal formation. Bead curvature was thought to contribute to the formation of hemi-synaptic specializations, preventing the modification of electrodes with flat contact points. To test this, we used cubic micro-hydrogels to show that hemi-synaptic specializations readily form onto flat dPGA coated surfaces. We propose that synthetic synaptogenic extracellular matrices that are resistant to proteolysis could be used to engineer electrodes with enhanced neural-biocompatibility and support bi-directional communication with neurons by directing the formation of stable synaptic specializations.

Disclosures: **T.A.J. Fisher:** None. **A. Shmuel:** None. **T.E. Kennedy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TE Kennedy is a co-founder of DendroTEK Biosciences, a company commercializing dPGA.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.04/E19

Topic: C.03. Parkinson's Disease

Support: PRIN 2022/PNRR P20222F4JY

Title: Alpha-synuclein oligomers disrupt brain barriers integrity via direct and immune-mediated mechanisms in Parkinson's disease

Authors: *C. BURGALETTO¹, G. GAUDIO¹, G. DI BENEDETTO¹, A. R. CARTA², R. BERNARDINI¹, G. CANTARELLA¹;

¹Dept. of Biomed. and Biotechnological Sci., Univ. of Catania, Catania, Italy; ²Dept. of Biomed. Sci., Univ. of Cagliari, Cagliari, Italy

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized, among other features, by α -synuclein (α Syn) misfolding and prominent neuroinflammation. Brain barriers (BBs), including both the blood-brain barrier and the choroid plexus, maintain central nervous system (CNS) homeostasis, thus their dysfunction is acknowledged as a key contributor to PD progression. To further investigate cellular and molecular mechanisms underlying BBs impairment, we assessed the direct effect of human α Syn oligomers (H- α SynOs) on BBs integrity, as well as their indirect impact via peripheral immune cells. Exposure of BBs models to H- α SynOs resulted in a significant reduction of BBs integrity, evidenced by decreased transendothelial/transepithelial electrical resistance (TEER), along with increased FITC-dextran permeability and uptake. Such changes were associated with altered expression of tight junction proteins, including ZO-1, Claudin-5, and Occludin. Concurrently, challenge with H- α SynOs brought about an elevation in pro-inflammatory cytokines IL-6 and IL-8, and a reduction of MCP-1 levels, mirroring the systemic scenario observed in human PD. To examine immune-mediated effects of H- α SynOs, isolated peripheral blood mononuclear cells (PBMCs) were exposed to the protein. BBs exposed to PBMCs conditioned media exhibited severe barrier breakdown. Interestingly, concomitant exposure of peripheral immune cells to both H- α SynOs and immunomodulatory agents partially restored barrier integrity and blunted the inflammatory scenario. Overall, these findings demonstrate that H- α SynOs compromise barriers function both through direct and immune-mediated mechanisms, highlighting BBs as potential targets for mitigating neuroinflammation, thus preserving CNS integrity.

Disclosures: C. Burgaletto: None. G. Gaudio: None. G. Di Benedetto: None. A.R. Carta: None. R. Bernardini: None. G. Cantarella: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.05/E20

Topic: C.03. Parkinson's Disease

Support: MCIN/AEI/FEDER PID2023-151392OB-I00
FPU21/01545
FPU018/02244

Title: Neuroprotection in an animal model of Parkinson's disease through systemic targeting of inhibitory immune checkpoint pathways

Authors: A. TAVIRA¹, C. VIDAURRE¹, L. BASURCO², M. A. ABELLANAS³, L. AYERRA¹, E. LUQUIN⁴, E. MENGUAL⁴, Á. VALES¹, G. GONZALEZ-ASEGUINOLAZA¹, S. HERVAS-STUBBS¹, M. SCHWARTZ², *M. AYMERICH⁵;

¹Cima-Universidad de Navarra, Pamplona, Spain; ²Departamento of Brain Sci., ³Dept. of Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel; ⁴Univ. de Navarra, Pamplona, Spain; ⁵CIMA - Univ. De Navarra, Pamplona, Spain

Abstract: Local brain inflammation is currently considered an important key contributor to Parkinson's disease (PD) progression, similar to other neurodegenerative diseases, alongside alpha-synuclein aggregation. It is not yet clear what drives this inflammatory process, and how it could be arrested. Emerging data from other neurodegenerative conditions suggest that these diseases are not confined to the brain, but also involve dysfunction of the immune system. Harnessing the peripheral immune system was found to be beneficial in arresting disease conditions in multiple models. Here, we hypothesized that this approach might be applicable to PD. We used a model of long-term alpha-synuclein overexpression in the nigrostriatal pathway of mice, using an adenoassociated virus as delivery vector (AAV- α -syn), which induced dopaminergic neuron loss, and motor deficits. We found that transient depletion of systemic regulatory T cells (Tregs) during the active phase of neurodegeneration reduced severity of disease manifestation following α -syn overexpression. These results encouraged us to adopt the therapeutic approach of transiently blocking the inhibitory PD-1/PD-L1 immune checkpoint pathway, previously found to be effective in animal models of dementia, including amyloidosis and tauopathy, through a mechanism involving recruitment of monocyte-derived macrophages and Tregs to the brain. We found that a single systemic treatment with anti-PD-L1 antibody, administered 2 or 3 weeks after AAV- α -syn injection, led to improved motor function, as assessed 5 or 6 weeks later using the pole and bar tests. In addition, we observed a robust protective effect on the survival of dopaminergic neurons. Overall, this therapeutic approach appears to be clinically translatable, suggesting that Parkinson's disease—like other neurodegenerative disorders—may be amenable to therapies targeting immune checkpoints.

Disclosures: A. Tavira: None. C. Vidaurre: None. L. Basurco: None. M.A. Abellanas: None. L. Ayerra: None. E. Luquin: None. E. Mengual: None. Á. Vales: None. G. Gonzalez-Aseguinolaza: None. S. Hervas-Stubbs: None. M. Schwartz: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CSO and cofunder of ImmunoBrain. M. Aymerich: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.06/E21

Topic: C.03. Parkinson's Disease

Support: American Parkinson's Disease Association

Title: Sars-cov-2 respiratory confinement does not to exacerbate mptp-induced nigrostriatal degradation

Authors: *H. CROY¹, S. AKULA³, J. B. EELLS²;

¹Comparative Biomed. Sci., ²North Carolina Univ., Raleigh, NC; ³East Carolina Univ., Greenville, NC

Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has demonstrated neurotropism and infiltration of the blood brain barrier (BBB), suggesting its possible role in accelerating neurodegenerative diseases, particularly Parkinson's Disease (PD). PD is characterized by the depletion of dopamine neurons (DN) in the substantia nigra pars compacta (SNpc) and the presence of muscle rigidity, declined motor coordination, and tremors. 10-15 years prior to a clinical diagnosis, during the prodromal stage, patients experience symptoms such as depression, muscle weakness, hyposmia, and ageusia, which overlap with symptoms observed in patients with post-acute sequelae of COVID-19 (PASC), where residual symptoms remain 6 weeks post infection. Previous studies have shown infiltration of the SNpc during acute infection, however, the long-term sensitivity of DNs in the absence of BBB disruption remains unknown. To investigate whether peripheral SARS-CoV-2 infection sensitizes SNpc DNs to degeneration, we utilized a mouse model expressing human ACE2 selectively in respiratory epithelium via intranasal administration of a modified AAV2/7-hACE2 vector, which enables respiratory confinement of the virus. Mice were then exposed to SARS-CoV-2 or mock treatment and subsequently given MPTP, a mitochondrial complex I inhibitor known to induce PD-like pathology. Quantification of TH positive neurons in the SNpc across Bregma levels - 2.54 to -2.62 revealed no significant difference in DN loss between SARS-CoV-2 MPTP and Mock MPTP groups. These findings suggest that in the absence of direct neuroinvasion or BBB infiltration, peripheral SARS-CoV-2 infection does not exacerbate MPTP-induced nigrostriatal degeneration.

Disclosures: H. Croy: None. S. Akula: None. J.B. Eells: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.07/E22

Topic: C.03. Parkinson's Disease

Title: Relevance of neuroinflammation in the exacerbation of dopamine neurotoxicity by N/OFQ and its receptor NOP

Authors: *K. RODRIGUEZ¹, J. E. PINTAR², A. W. KUSNECOV¹;

¹Psychology, ²Neurosci. & Cell Biol., Rutgers Univ., Piscataway, NJ

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic (DA) neurons in the substantia nigra (SN). A pathological hallmark of PD is the formation of Lewy bodies, associated with alpha-synuclein (α -syn)-mediated neurotoxicity. It has been hypothesized that accumulation of the DA metabolite DOPAL and its interactions with α -syn may amplify neurotoxic effects, though its role in neurodegeneration via inflammatory signaling remains poorly understood. Further, recent studies have explored the involvement of the neuropeptide nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) in PD pathology, with evidence suggesting that N/OFQ-NOP signaling, under conditions of cell stress, may exacerbate DA neuron degeneration by influencing microglial activation. To investigate the role of NOP in dopaminergic toxicity, we compared DA cell survival and microglial activation in wildtype and NOP knockout (KO) mice treated with DOPAL or 6-OHDA, a well-known DA cell neurotoxin. In contrast to previous findings, we observed that in response to 6-OHDA, the absence of NOP exacerbated dopaminergic loss and led to the manifestation of motor and non-motor symptoms associated with PD. Furthermore, our study revealed that in WT and NOP-deficient mice, DOPAL administration did not produce behavioral changes that differed from controls. Although the dose of DOPAL was low, it may not be a suitable model for PD in comparison to the well-established 6-OHDA model. Importantly, these results highlight the critical role of NOP signaling in PD pathology and suggest its potential as a therapeutic target.

Disclosures: K. Rodriguez: None. J.E. Pinter: None. A.W. Kusnecov: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.08/E23

Topic: C.03. Parkinson's Disease

Support: General Secretariat for Research and Innovation under the action TAA
TAEDR-0535850 - BrainPrecision [European Union (NextGenerationEU)
National Recovery and Resilience Plan Greece 2.0]
Hellenic Pasteur Institute postdoctoral fellowship

Title: Microglia-specific early phenotypic and functional changes upon neuronal expression of familial Parkinson's disease p.A53T-alpha-synuclein

Authors: *E. NINO¹, A. DECZKOWSKA³, E. TAOUFIK²;

¹Mol. and Cell. Neurobio. Lab., ²Hellenic Pasteur Inst., Athens, Greece; ³Inst. Pasteur Paris, Paris, France

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder (ND), characterized by diverse clinical manifestations. Synaptic dysfunction, a hallmark of most NDs, arises from structural and functional synaptic changes that can act as both a cause and a consequence of the disease. Recent evidence suggests a neurodevelopmental origin for synaptic dysfunction, challenging the long-held view that it emerges as a late-stage phenomenon. These findings underscore the role of inappropriate glial interactions, not only in adulthood but also during critical embryonic and postnatal developmental stages, where microglia are known to play pivotal roles.

In this study, we employ the M83 mouse model, which overexpresses human p.A53T-alpha Synuclein (p.A53T α Syn) in neurons, a mutation linked to autosomal dominant familial PD. Transcriptomic analysis of microglia from A53T mice at postnatal day 7, well before the onset of any observable symptoms, reveals over 650 differentially expressed genes (DEGs) compared to wild-type (WT) microglia, the vast majority of them downregulated. This finding highlights significant early molecular alterations in microglial signaling pathways associated with PD pathogenesis. Notably, genes associated with the type I interferon (IFN-I) response were significantly upregulated, suggesting that an early IFN response is a key feature of microglial activation in this model, possibly triggered by immunostimulatory dsRNA species formed in neurons.

Moreover, morphological, histochemical, and functional analysis of microglia across multiple brain regions at key developmental and disease stages—embryonic (E14-E17), early postnatal (P7-P10), young adult (P30), older adult (4-5 months), and symptomatic (>1 year)—reveal a potential exhaustion of microglia starting from the earliest stages of disease.

This study leverages the p.A53T α Syn familial PD model to investigate neuron-microglia interactions during the earliest and presymptomatic phases of PD. By adopting a non-neurocentric approach, we aim to elucidate the role of microglia in disease progression, define disease-associated cellular subpopulations, and identify potential therapeutic targets.

Funded by the General Secretariat for Research and Innovation under the action TAA TAEDR-0535850 - BrainPrecision [European Union (NextGenerationEU); National Recovery and Resilience Plan Greece 2.0]; Hellenic Pasteur Institute postdoctoral fellowship awarded to EN.

Disclosures: E. Ninou: None. A. Deczkowska: None. E. Taoufik: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.09/E24

Topic: C.03. Parkinson's Disease

Support: FONCYT PICT-2019-2019-02114
UBACYT 20020220300138BA

Title: Microglial dynamics during synaptic spine loss after nigrostriatal injury

Authors: *F. FARES TAIE¹, A. G. LEÓN², A. M. STAHL¹, D. E. PAFUNDO¹, J. E. BELFORTE¹, M. G. MURER¹, I. R. E. TARAVINI³, L. RELA¹;
¹IFIBIO Houssay UBA-CONICET, Buenos Aires, Argentina; ²Univ. of Buenos Aires, Buenos Aires, Argentina; ³ICTAER CONICET-UNER, Gualeguaychu, Argentina

Abstract: Parkinson's disease (PD) patient postmortem tissue analysis reveals striatal medium spiny neuron (MSN) dendritic spine loss and microglial reactivity, both also observed in animal models. Microglia-mediated spine pruning was demonstrated in other scenarios, yet remains virtually unaddressed in PD models. To approach this, we studied the time course of spine loss and microglial reactivity in experimental hemi-parkinsonism. Hemi-parkinsonian female C57BL/6 mice (4 months old on average) were generated by unilateral 6-hydroxydopamine injection into the medial forebrain bundle. Sparse MSN labeling was achieved by retro-orbital PHP.eB-AAV-GFP vector administration. We analyzed microglial reactivity after Iba1 immunostaining and MSN spine density at 1, 2 and 4 weeks post-lesion (W1, W2, W4, n=5 animals/group). Microglial cell density significantly increased in the ipsilateral striatum at W1 vs. the contralateral side (417 ± 22 vs. $286 \pm 10/\text{mm}^2$, $p < 0.0001$, post-hoc test in 2-way RM-ANOVA), returning to contralateral values by W2 (311 ± 7 vs. $287 \pm 6/\text{mm}^2$, $p = 0.181$). Inter-cell distance analysis showed transient ipsilateral microglial clustering (overrepresentation of distances $< 16 \mu\text{m}$), predominantly at W1 ($p < 0.0001$, Chi Square), consistent with local proliferation. Sholl analysis after 3D reconstruction of microglia (at least 20 cells/group) revealed decreased ipsilateral complexity at W1-2, not observed by W4 (cumulative intersections: W1, 51 ± 4 vs. 90 ± 4 ; W2, 54 ± 3 vs. 83 ± 4 ; $p < 0.0001$ for both, post-hoc test in 2-way ANOVA). Soma volume was larger on the lesioned side at all time points (W1, 255 ± 22 vs. $157 \pm 12 \mu\text{m}^3$; W2, 214 ± 16 vs. $175 \pm 8 \mu\text{m}^3$; W4, 204 ± 19 vs. $161 \pm 15 \mu\text{m}^3$; $p < 0.0001$, lesion factor in 2-way ANOVA). Exploratory MSNs spine density analysis showed detectable pruning by W2 (14 ± 0.78 spines/ $10 \mu\text{m}$ vs. expected reference, $p = 0.0078$, one sample Wilcoxon test). 2D-colocalization analysis of Intracellular GFP in microglia suggested an elevation in engulfment activity, indistinguishable between sides at W1-2, that declined contralaterally by W4 (colocalized area: $5.0 \pm 0.9\%$ vs. $0.8 \pm 0.3\%$, $p = 0.0004$, post hoc test in 2-way ANOVA). Data are mean $\pm$ SEM. These findings suggest that the microglial response after dopaminergic denervation is fast and consists of short-term (hyperplasia), intermediate (decreased complexity and phagocytosis) and longer term (soma hypertrophy) components. Its timing is compatible with microglia-mediated phagocytosis of MSN dendritic spines. Our data highlights the importance of time-resolved analyses to identify critical windows of intervention to determine a causal role of microglia in parkinsonism-related plasticity.

Disclosures: F. Fares Taie: None. A.G. León: None. A.M. Stahl: None. D.E. Pafundo: None. J.E. Belforte: None. M.G. Murer: None. I.R.E. Taravini: None. L. Relá: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.10/E25

Topic: C.03. Parkinson's Disease

Support: NSTC 113-2320-B-039 -006, Taiwan

Title: Neurotoxin MPTP enhances the binding of WWOX with Parkin to activate ERK and SMAD promoter to promote neurodegeneration

Authors: *N.-S. CHANG;
China Med. Univ., Taichung, Taiwan

Abstract: Deficiency of the *WWOX/Wwox* gene in newborns leads to severe neural diseases and early death. Functional pY33-WWOX limits the progression of Alzheimer's disease (AD). Neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺) upregulates pY33-WWOX to cause apoptosis in many cells, and increases the binding of pY33-WWOX with Parkin, an E3 ligase, as determined by yeast two-hybrid analysis, Förster resonance energy transfer (FRET) microscopy, proximity ligation assay, and co-immunoprecipitation. The binding of Parkin to the N-terminus of WWOX (WWOX7-21) activates ERK to increase SMAD promoter activation for causing apoptosis. 17β-estradiol (E2) dissociates the WWOX/Parkin complex to abolish cell death. MPTP, a precursor of MPP⁺, upregulates the disease-promoting pS14-WWOX and reduces the dopaminergic neurons in the substantia nigra of the wild-type B6 mice. Loss of dopaminergic neurons and reduction in the width of striatopallidal fibers occurs in the *Wwox* heterozygous and knockout mice. Neuroprotective Zfra4-10 or WWOX7-11 (or 7-21, 4-17) peptide significantly mitigates the effect of MPTP and pentylenetetrazol (PTZ). When male mice received Zfra4-10 or WWOX7-11 peptide, they resisted PTZ-induced seizures and exhibited proper behavioral responses in pole test and open field analysis. Zfra4-10/WWOX7-11-treated mice suffered PTZ-mediated seizures. Zfra4-10/WWOX7-11 only upregulated the PD marker α-synuclein, inflammatory microglia IBA1, and AD-promoting pS14-WWOX, and downregulated the functional glycosylated dopamine transporter (DAT), along with poor performance in behavioral tests. Together, MPTP induces Parkin/pY33-WWOX complex formation for ERK activation and SMAD promoter activation and apoptosis. The Parkin/pY33-WWOX complex is dissociated by Zfra, thereby facilitating neurodegeneration due to upregulated α-synuclein, IBA1, and pS14-WWOX and downregulated functional DAT.

Disclosures: N. Chang: None.

Poster

PSTR016: Parkinson's Disease: Neuroinflammation and Immune Actions

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR016.11/E26

Topic: C.03. Parkinson's Disease

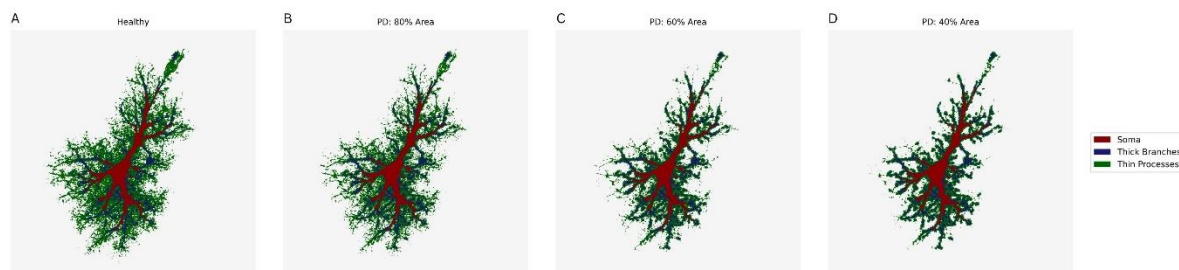
Title: A computational tool to create morphologically accurate astrocytes at various stages of Parkinson's Disease pathogenesis for use in simulations

Authors: R. GUHA¹, K. TAKAHASHI², *B. GUHA³;

¹Del Norte High School, San Diego, CA, San Diego, CA; ²Ruten Inc., Naperville, IL;

³Independent, San Diego, CA

Abstract: Parkinson's disease (PD) is a neurodegenerative disease that causes astrocytic atrophy, with final stages characterized by maximum retention of 40% of total astrocytic surface area and 55% of total perimeter (Ramos-Gonzalez et al. 2021). Astrocytic morphological regions are categorized into soma, thick branches, thin processes, and extracellular space by astrocytic volume fraction (AVF). Most atrophy occurs in the thin processes, which impairs gliotransmission. Despite the proven impact of astrocytic dysfunction on PD, currently, there are no experimental or computational methods that depict progressive morphological decline in the same astrocyte over PD stages. Our project uses image processing and computational modeling to create simulation-ready astrocyte images with progressive atrophy. Healthy astrocyte images (Cell Image Library, n=27, Figure 1A) were preprocessed (upscaled and colorized) and thresholded into AVF masks by intensity. Each image was rescaled based on pixel-to-micron spatial grid conversions to meet Courant-Friedrichs-Lewy conditions. PD variants with 80%, 60%, and 40% of healthy area retained (Fig. 1B-D) were created via power-law-based pruning of thin processes for each astrocyte. The quasi-deterministic pruning introduces stochastic variability; regenerated PD morphologies from the same input exhibit biologically plausible differences. Our tool-generated images of healthy and PD astrocytes display significant, discernible morphological atrophy. To validate morphological fidelity, we ran identical Ca^{2+} wave simulations for each astrocyte at each PD stage. Wave characteristics (speed and decay time constants) varied significantly in accordance with expected PD trends at each atrophied stage (ANOVA, $p < 0.01$). This validates that our novel images allow for accurate representation of functionally distinct, disease-relevant astrocytic states. Our tool has the potential to enable further simulations of PD astrocytic conditions and can be adapted to create and simulate networks of PD astrocytes to test therapeutic methods.



Disclosures: R. Guha: None. K. Takahashi: None. B. Guha: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.01/E27

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: H2020-MSCAITN-2019-EJD - grant agreement no: 860070
DFG BR1192/14-2

Title: Identification of polypharmacological drug candidates that restore physiological tau-microtubule interaction by quantitative live cell imaging

Authors: L. PINZI¹, C. CONZE², N. BISI¹, A. SOLIMAN³, N. MONTEIRO ABREU³, N. TRUSHINA³, M. KHODAEI DOLOUEI³, A. HELLWIG⁴, M. CHRISTODOULOU⁵, D. PASSARELLA⁵, L. BAKOTA³, G. RASTELLI¹, ***R. BRANDT**³;

¹Univ. of Modena and Reggio Emilia, Modena, Italy; ²Leibniz Inst. of Virology (LIV), Hamburg, Germany; ³Osnabrueck Univ., Osnabrück, Germany; ⁴Univ. of Heidelberg, Heidelberg, Germany; ⁵Univ. of Milan, Milan, Italy

Abstract: Alzheimer's disease and other tauopathies are characterized by aggregation, increased phosphorylation, and impaired microtubule interaction of the microtubule-associated protein tau. Pathological changes in tau are closely associated with neurodegeneration, making tau a prime candidate for intervention. While immunotherapy-mediated degradation of tau represents a promising therapeutic strategy, its clinical application is limited by the high antibody doses required and the associated potential for adverse effects. To overcome these challenges, we investigated small molecules with polypharmacological activity as a potentially safer and more effective alternative. We developed a live-cell imaging technique with fluorescence decay after photoactivation (FDAP) to monitor the interaction of tau with microtubules in axon-like processes, as well as live staining with the optotracer Amytracker, that detects amyloids of at least eight molecules, to determine tau aggregation. Alterations in the phosphorylation profile of tau and changes in the signal transduction mechanism were determined by phosphoproteome analysis. We show that the formation of tau aggregates in the cell body of neurons correlates with reduced interaction of tau with axonal microtubules. We tested a series of 2-phenyloxazole derivatives as potential polypharmacological small molecules that interact with tau and modulate tau kinases. Importantly, these compounds were also assessed for potential cytotoxicity. The most active derivative inhibited tau aggregation in the micromolar range in the absence of cytotoxicity and restored physiological microtubule interaction of tau in the neuronal processes. Phosphoproteome analysis showed a significant reduction in the phosphorylation profile, particularly at sites in the regulatory proline-rich region of tau, indicating polypharmacological activity. Systematic modification of side groups of the lead compound enabled the modulation of cellular activities. Our data demonstrate that live-cell imaging of a tauopathy model enables the systematic characterization and optimization of polypharmacological drug candidates that simultaneously inhibit tau aggregation and modulate tau phosphorylation.

Disclosures: L. Pinzi: None. C. Conze: None. N. Bisi: None. A. Soliman: None. N. Monteiro Abreu: None. N. Trushina: None. M. Khodaei Dolouei: None. A. Hellwig: None. M. Christodoulou: None. D. Passarella: None. L. Bakota: None. G. Rastelli: None. R. Brandt: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.02/E28

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Maytansinoid-derived PROTACs induce tubulin degradation in peripheral model neurons without affecting the physiological tau-microtubule interaction

Authors: G. NORDIO¹, L. SINGH², L. ALVES BORBA², A. MAIOCCHI³, D. PASSARELLA⁴, R. BRANDT², ***L. BAKOTA**²;

¹Univ. of Padua, Padua, Italy; ²Osnabrück Univ., Osnabrück, Germany; ³Univ. of Milan, Milan, Italy; ⁴Univ. of Milan, Milano, Italy

Abstract: Nerve damage, referred to as peripheral neuropathy, is frequently associated with current microtubule-targeting cancer therapies and significantly limits their efficacy. Here, we investigate the potential of PROTACs (Proteolysis Targeting Chimeras) to degrade $\alpha\beta$ -tubulin as a possible alternative microtubule-targeting cancer therapy with the benefit of reducing peripheral neuropathy. PROTAC-mediated tubulin degradation may also have the potential to reverse the disruptive effects of microtubule-stabilizing drugs used to treat solid tumors and restore normal microtubule dynamics in neuronal cells. We investigated four PROTACs to degrade the $\alpha\beta$ -tubulin heterodimer in peripheral model neurons, using the microtubule-destabilizing drug maytansine to bind tubulin. Each PROTAC linked maytansine via linkers of varying lengths to either lenalidomide or VH032—ligands that recruit specific E3 ligases. We investigated the efficacy of these PROTACs in inducing tubulin degradation and maintaining the stability of the remaining microtubules. We used dot blot analysis, examined both acetylated and total tubulin, determined compound toxicity using MTT and LDH assays, performed morphological analysis of neurite formation, and measured tau-microtubule interaction using quantitative live-cell imaging. Finally, mass spectrometry was used to determine whether specific tubulin isoforms exhibit different degradation rates. We identified a lead candidate, AM93, which induced significantly reduced tubulin content in low micromolar range without toxicity or disruption of mitochondrial function. Reduced tubulin was associated with increased relative microtubule stability, suggesting preferential degradation of soluble tubulin and labile microtubules. While AM93 did not alter the overall length of cell processes, it induced a slight increase in the number of shorter neurites. Importantly, tau protein binding to microtubules in axon-like cell processes remained unchanged. The data suggest that tubulin-targeting PROTACs could be a useful approach for targeted cancer treatment, as they may exhibit lower toxicity to peripheral neurons than currently used microtubule-stabilizing drugs.

Disclosures: G. Nordio: None. L. Singh: None. L. Alves Borba: None. A. maiocchi: None. D. passarella: None. R. Brandt: None. L. Bakota: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.03/E29

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: R21AG081907

Title: Inhibition of endosomal microautophagy increases respiration and glycolysis in human neuronal cultures

Authors: *E. E. CONGDON¹, C. Ji¹, E. M. SIGURDSSON^{1,2};

¹Dept of Neuroscience, Inst. for Translational Neurosci., ²Dept. of Psychiatry, New York Univ. Grossman Sch. of Med., New York, NY

Abstract: Endosomal microautophagy (eMi) has been understudied compared to other protein digestion pathways. Dysfunction of eMi impairs synaptic transmission, protein turnover, and potentially promotes spreading of tau pathology, making it of special concern in Alzheimer's disease (AD). Thus, investigating how tau pathology and eMi impact each other will increase our understanding of AD pathogenesis and potentially identify targets for intervention. We generated human neuronal cultures from induced pluripotent stem cell lines obtained from the NINDS repository expressing either P301L mutant human tau or its isogenic control to examine the impact of both endogenous tau expression and the effects of acute exposure to tauopathy patient-derived paired helical filament (PHF) tau on eMi and cellular processes. In neurons expressing fluorescent KFERQ peptide (an eMi substrate), the number of positive puncta increased in neurons incubated with 1 µg/ml PHF. Western blotting also showed an increase in markers of multivesicular bodies (MVB), indicating increased eMi activity under these conditions. Because reduced expression of ATP-synthase and production of reactive oxygen species (ROS) can alter eMi, and both of these may be affected by tau, we also examined the impact of tau on mitochondria in the human neurons. Using tetramethylrhodamine (TMRM) fluorescence to quantify mitochondrial membrane potential, we found that cells expressing mutant tau had a lower baseline membrane potential ($p < 0.0001$). Addition of 1 µg/ml of PHF significantly reduced fluorescence ($p < 0.0001$), with the P301L neurons showing a greater reduction compared to its isogenic line ($p < 0.0001$). We also added dihydroethidium (DHE) to the cultures to examine the production of ROS. In both lines, DHE fluorescence increased to a similar extent in the presence of 1 µg/ml of PHF ($p = 0.05 - < 0.0001$). Additionally, we conducted Seahorse mitochondrial stress testing. In both lines, incubation with 1 µg/ml PHF significantly reduced baseline respiration, as measured by oxygen consumption rate and glycolysis ($p = 0.03 - < 0.0001$). To determine whether increasing ATP-synthase activity or reducing ROS could normalize eMi, we incubated cells with either PRE-084 or Trolox. Neither treatment prevented the PHF-induced increase in KFERQ positive puncta or MVB markers. However, when eMi was inhibited by siRNA, oxygen consumption rate and glycolysis were normalized in mitochondrial stress testing. These data show how exposure to pathological tau can destabilize energy

production and protein digestion, and that blocking acute eMi activation reduced the detrimental impact of tau pathology on mitochondria.

Disclosures: **E.E. Congdon:** None. **C. Ji:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapies and related diagnostics that are assigned to New York University.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.04/E30

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant NS113763
NIH Grant AG079797
NIH Grant NS127728
NIH Grant AG067597

Title: Generation of human induced pluripotent stem cell-derived cortical neurons expressing the six tau isoforms

Authors: H. JIANG, Z. XIAO, K. SALEEM, P. ZHONG, L. LI, G. CHHETRI, P. LI, Z. JIANG, Z. YAN, ***J. FENG**;

Dept. of Physiol. and Biophysics, State Univ. of New York at Buffalo, Buffalo, NY

Abstract: The alternative splicing of *MAPT*, which encodes Tau, in the adult human brain produces six major isoforms that play critical roles in the pathogenesis of tauopathies including Alzheimer's disease. Previous efforts have failed to differentiate human induced pluripotent stem cells (hiPSCs) to cortical neurons expressing the six isoforms of Tau. We searched for the optimal concentration, duration, and treatment window of morphogens in the differentiation of hiPSCs through embryoid bodies (EBs) to dorsal forebrain neuroepithelial cells, then to cortical neurons. The combined inhibition of WNT, SHH, and SMAD signaling in EBs generated neuroepithelial cells expressing appropriate dorsal forebrain markers, while suppressing ventral, midbrain, and hindbrain genes. Further differentiation in neurogenic and neurotrophic factors produced MAP2⁺ neurons at day 18. The iPSC-derived neurons expressed markers of all cortical layers and exhibited synapse formation and synaptic physiology. In addition, MAP2⁺ neurons and mitotic cells expressing radial glial markers formed aggregates that could be dissociated to produce mature neurons with similar properties. Most importantly, the six Tau isoforms were expressed from day 80 in a developmentally regulated manner, modeling the situation in human brains on an accelerated timeline. This chemically defined differentiation method produces a key hallmark of mature human cortical neurons by expressing the six main splicing isoforms of Tau.

It will greatly facilitate disease modeling and therapeutic discovery for many human brain disorders involving cortical neurons.

Disclosures: H. Jiang: None. Z. Xiao: None. K. Saleem: None. P. Zhong: None. L. Li: None. G. Chhetri: None. P. Li: None. Z. Jiang: None. Z. Yan: None. J. Feng: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.05/E31

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant R00AG073455
NIH Grant K99AG073455

Title: Mutant α -tubulins rescue neurodysfunction and neurodegeneration in transgenic tauopathy models

Authors: *S. J. Z. BENBOW^{1,2,3}, R. UHRICH⁴, A. SAXTON⁴, A. BEALE², P. J. MCMILLAN⁵, C. A. DAHLEEN², R. L. KOW⁴, B. C. KRAEMER^{6,5,2,3};
¹UW Sch. of Med., Seattle, WA; ²Seattle Inst. for Biomed. and Clin. Res., Seattle, WA; ³Grecc, ⁴GRECC, VA Puget Sound Healthcare Syst., Seattle, WA; ⁵Dept Psychiatry & Behavioral Sci., Univ. of Washington, Seattle, WA; ⁶Div. of Geriatrics and Gerontology, Univ. of Washington Sch. of Med., Seattle, WA

Abstract: Lesions containing misfolded and aggregated tau protein are characteristic of tauopathies, age-related neurodegenerative diseases such as Alzheimer's disease, for which no cures exist. Transgenic *C. elegans* models for tauopathy, which express human tau pan-neuronally, recapitulate several features of human disease including motility deficits indicative of neurodysfunction, progressive tau aggregation, neuron loss, and shortened lifespan. They provide a uniquely genetically tractable system through which to study mechanistic disease progression. Forward genetic screening using *C. elegans* models has led to the discovery of several genetic suppressors of pathological tau within unique mechanistic pathways. Through such screens, we have discovered several mutant α -tubulin genes that modify tau-induced phenotypes in transgenic *C. elegans* models. α -tubulin and β -tubulin heterodimers are the building blocks of microtubules, dynamic, tube-shaped polymer proteins that play crucial roles in the maintenance of cell structure and tracks for motor-driven transport. Tau is a microtubule associated protein and regulator of neuronal microtubules. Microtubule dysregulation has been hypothesized to play a role in the progression of tauopathies, though the specific toxic mechanisms have remained unclear. Mutations in the α -tubulin genes *tba-1*, *tba-2*, and *mec-12* suppress human tau-induced motility deficits and neurodegeneration in our transgenic nematode tauopathy models suggesting that altered tau-microtubule interactions may play a role in

pathogenesis. To understand the underlying mechanisms driving mutant tubulin mediated suppression of tau toxicity we examined levels of tubulin gene expression, levels of total tau protein, tau phosphorylation and tau aggregation as well as microtubule properties and tau-microtubule interactions. Together, these studies serve to elucidate whether the mechanisms of mutant tubulin suppression of tau induced pathology are based in changes to tau-microtubule interactions and will contribute to a greater understanding of the roles of the cytoskeleton in neurodegenerative disease.

Disclosures: S.J.Z. Benbow: None. R. Urrich: None. A. Saxton: None. A. Beale: None. P.J. McMillan: None. C.A. Dahleen: None. R.L. Kow: None. B.C. Kraemer: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.06/Web Only

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH grant R21 AG058282 (E.M.S.)
R01 AG032611 (E.M.S.)
R01 NS077239 (E.M.S.)
R01 NS120488 (E.M.S.)
Alzheimer's Association Research Fellowships [AARF-22-924783 (Y.J.)
Alzheimer's Association Research Fellowships AARF-22-926735 (C.J.)

Title: Single-domain antibody-based autophagosome-targeting chimera for tau clearance and motor function improvement in tauopathies

Authors: *Y. JIANG¹, A. M. TETLOW¹, Y. LIN¹, C. JI¹, C. F. LABORC¹, A. C. MAR¹, R. PAN², X.-P. KONG², E. E. CONGDON¹, E. M. SIGURDSSON^{1,3};

¹Department of Neuroscience, Inst. for Translational Neurosci., ²Dept. of Biochem. and Mol. Pharmacol., ³Dept. of Psychiatry, New York Univ. Grossman Sch. of Med., New York Univ. Grossman Sch. of Med., New York, NY

Abstract: Tauopathies are neurodegenerative diseases marked by pathological tau accumulation, yet effective tau-targeting therapies remain elusive. We developed a modified 1D9 (m-1D9), a single-domain antibody (sdAb)-based degrader that promotes tau clearance via the autophagy-lysosomal pathway. This molecule fuses anti-tau sdAb 1D9 with a modified LC3-interacting region (LIRΔTP53INP2) to recruit tau to autophagosomes. In cortical neurons derived from frontotemporal dementia patient iPSCs carrying the P301L mutation, the m-1D9 (50 nM, 3 days) reduced total tau (CP27) by 41% and phospho-tau by 82% and 68% (PHF1 and pSer199) vs. control (all p < 0.001). Under these conditions, the unmodified 1D9 was ineffective in clearing tau. No significant changes were observed in NeuN or GAPDH levels, indicating no toxicity of

the treatment. Mechanistically, the tau clearing effect of m-1D9 was blocked by lysosomal inhibitor Baf.A1 but not by proteasomal inhibitor MG132 (ANOVA, $p = 0.0012$). Specifically, m-1D9 reduced total tau by 59% (25 nM, 2 days, $p = 0.0104$), which was blocked by Baf.A1 ($p = 0.0172$) but not MG132 ($p > 0.9999$), indicating lysosome-dependent degradation. Immunofluorescence showed increased tau-LC3B colocalization (+357% vs. control, $p = 0.0012$; +333% vs. 1D9, $p = 0.0013$; ANOVA, $p = 0.0007$), supporting autophagic engagement. In co-immunoprecipitation assay, m-1D9 enhanced tau-LC3B interaction, confirming ternary complex formation. To determine in vivo target engagement and efficacy, 8-month-old homozygous female JNPL3 mice (P301L tau) received a single intravenous (IV) injection of fluorescently-tagged 1D9 or m-1D9 (700 nmol/kg). Both sdAbs entered the brain and spinal cord, where confocal imaging confirmed colocalization with PHF1 stained tau aggregates and LC3B. Weekly IV injections over 6 weeks (vehicle, 1D9, m-1D9; $n = 25$ total; 200 nmol/kg) showed that m-1D9 improved stride length by 15% ($p = 0.0037$) and reduced lateral paw support by 87% ($p = 0.0473$) vs. control. Biochemically, it decreased soluble phospho-tau by 60% and 49% (PHF1, $p = 0.0003$; AT8, $p = 0.0002$) and insoluble tau by 37% ($p = 0.0221$) vs. control, while sparing total soluble tau. GFAP and Iba1 were reduced by 41% ($p = 0.0061$) and 71% ($p < 0.0001$) vs. control. Immunohistochemistry revealed extensive tau pathology in control JNPL3 mice that was reduced by 86% by m-1D9 treatment (MC1, $p = 0.0025$). Under these conditions, unmodified 1D9 had no efficacy in vivo. These results support sdAb-based degraders as potent, brain-penetrant therapeutics for tauopathies.

Disclosures: Y. Jiang: None. A.M. Tetlow: None. Y. Lin: None. C. Ji: None. C.F. Laborc: None. A.C. Mar: None. R. Pan: None. X. Kong: None. E.E. Congdon: None. E.M. Sigurdsson: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); E.M.S. is an inventor on a patent application related to the initial development of anti-tau sdAbs filed by New York University.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.07/E32

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Robert A. and Reneé E. Belfer Family Foundation
Oskar Fischer Project
Bowes Family Foundation

Title: The nucleoside reverse transcriptase inhibitor 3TC ameliorates tau-mediated hippocampal neuroinflammation in tau transgenic mice

Authors: *Z. UTTKE¹, P. RAMIREZ¹, K. ALLTON², J. MA², W. J. RAY², B. FROST¹;
¹Brown Univ., Providence, RI; ²MD Anderson, Houston, TX

Abstract: Accumulating evidence points to neuroinflammation as a primary driver of age-related neurodegenerative disorders, including Alzheimer's disease and related tauopathies. Recent studies report that nucleoside reverse transcriptase inhibitors (NRTIs) significantly reduce neurodegeneration in in vivo and cellular models of tau-mediated neurodegeneration. We recently completed a phase IIa clinical trial establishing the safety and tolerability of the NRTI Lamivudine (3TC) in a cohort of participants with early Alzheimer's disease and found significant reduction of GFAP, an indicator of reactive astrocytes, in cerebrospinal fluid after six months of treatment. Recent epidemiological analyses further suggests that exposure to NRTIs reduces the risk of developing Alzheimer's disease. Despite the early involvement and vulnerability of the hippocampus in tauopathies, the effects of NRTIs on the hippocampus remains underexplored. To bridge this gap, we investigated the effects of 3TC on hippocampal neuroinflammation in two mouse models of tauopathy. RNA sequencing of micro-dissected hippocampal tissue from rTg4510 and PS19 mice revealed elevation of neuroinflammatory gene transcripts as a consequence of transgenic tau expression, and that neuroinflammation is significantly suppressed by a 4-week oral intervention of 3TC. Deconvolution of bulk transcriptomic data using the Allen Institute's single-cell RNA sequencing atlas suggests that 3TC significantly reduces the elevation of astrocytes in the hippocampi of tau transgenic mice. Taken together, our analyses support the growing evidence that NRTIs may play a valuable therapeutic role in neurodegenerative disorders.

Disclosures: **Z. Uttke:** None. **P. Ramirez:** None. **K. Allton:** None. **J. Ma:** None. **W.J. Ray:** None. **B. Frost:** None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.08/E33

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: T32 Training Grant - Precision Genetics of Aging and Dementia
JAX Director's Innovation Fund

Title: Expressing humanized tau isoforms in the prelimbic cortex alters the synaptic connectivity of cortical neurons

Authors: ***E. W. NICKERSON**, E. B. BLOSS;
The Bloss Lab., The Jackson Lab., Bar Harbor, ME

Abstract: Abnormal accumulation of the microtubule binding protein tau is the defining characteristic of a diverse set of neurodegenerative diseases, collectively called tauopathies. Tauopathies can be differentiated by which of the six tau isoforms are present, suggesting that the structure of tau may dictate disease progression. Yet, exactly how altered forms of tau drive

dysfunction is unknown. Previous studies have demonstrated that overexpression of mutant humanized tau (hTau) can impair cellular function, but such work often present conflicting reports that may reflect the difficulty of comparing models confounded by off-target effects or their use of different hTau isoforms and mutations. We developed a viral strategy to address this gap which enables us to express one of several disease linked mutations in the context of two different hTau isoforms and in the same set of cortical neurons across mice. P301L, A152T, and R406W are in different functional domains of hTau, providing an opportunity to distinguish between common and distinct mechanisms by which hTau drives dysfunction. To interrogate the relationship between hTau primary structure and intracellular function, we compared the binding partners of different hTau isoforms at somatodendritic and axonal sites by co-immunoprecipitating the protein complexes and analyzing them with tandem mass spectrometry. We found striking differences across the mutant and wild-type hTau proteins. For example, P301L had increased interactions with mitochondrial proteins and those associated with energy and metabolism. To evaluate how synaptic connectivity is affected by the expression of hTau, we reconstructed synaptic connections on prelimbic cortical neurons that project to the amygdala. Expressing either P301L or A152T hTau led to a significant decrease in spine density on apical and proximal dendrites. Moreover, we found evidence of spine morphological remodeling of the remaining spine populations. Taken together, these results suggest that disease-relevant mutations in hTau produce distinct effects on protein-protein interactions but generate similar effects on synaptic connectivity.

Disclosures: E.W. Nickerson: None. E.B. Bloss: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.09/E34

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Directly Reprogrammed Neurons Retain Donor Specific Tau Isoform Ratios

Authors: *M. PHAN¹, S. H. YUAN²;

¹Neurosci., Univ. of Minnesota, Minneapolis, MN; ²Neurol., Univ. of Minnesota, Twin Cities, Edina, MN

Abstract: Age is an independent risk factor for the development of neurodegenerative disorders which affect millions of individuals worldwide. One such category of neurodegenerative disorders is primary tauopathies, in which a major pathological hallmark is the aggregation of microtubule associated protein tau, suggesting failure in the maintenance of proper protein folding and homeostasis. Misfolded tau has been implicated in numerous neurodegenerative disorders including Alzheimer's Disease (AD) and Progressive Supranuclear Palsy (PSP), highlighting the importance of understanding how tau contributes to disease progression.

Perturbations in the unfolded protein response (UPR), a cellular mechanism responsible for maintenance of protein quality control, has been shown to affect levels of tau aggregation and misfolding. UPR function decreases as one ages, possibly contributing to increased misfolded protein and the development of neurodegeneration. However, the molecular mechanisms by which aging affects the UPR and protein homeostasis are not sufficiently understood. A genome-wide association study (GWAS) in PSP patients identified the risk variant p.D566V in the PERK (Protein Kinase R-like ER Kinase) gene, a transmembrane protein that senses endoplasmic reticulum (ER) stress and initiates the UPR. This risk variant is in linkage disequilibrium with three other Single Nucleotide Polymorphisms (SNPs) in the coding region, p.S136C, p.R166Q and p.S704A, also known as PERK risk-Haplotype B. We previously showed that UPR function and tau metabolism is altered in patient-derived Haplotype B neurons, suggesting genetic contribution to neurodegeneration pathogenesis. Induced neurons (iNs), a novel in vitro approach developed by Dr. Jerome Mertens at the University of California - San Diego, retains the patient's aging signature and epigenetics. To characterize the effectiveness of this novel protocol, confirming its ability to retain aging signatures as well as retain tau isoform ratios, we have begun developing and optimizing this protocol for its use with PSP patient and control fibroblasts. Preliminary qPCR data shows an increased ratio of 4R tau compared to 3R tau in the PSP patient line compared to a 1:1 ratio in the control line, matching the expected pathology of PSP. We will continue characterization by differentiating additional cell lines as well as performing RNA-sequencing to confirm the retention of aging markers as well as protein analysis for PERK-related pathological differences.

Disclosures: M. Phan: None. S.H. Yuan: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.10/E35

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant F31G082391
NIH Grant F99AG088436
NIH Grant RF1AG078374
VA Grant I01BX005742
VA Grant I01BX005762
NIH Grant R01AG084552

Title: The ubiquitin ligase adaptor SPOP contributes to tau aggregation, neurodegeneration, and cognitive deficits in a mouse model of tauopathy

Authors: *R. ECK¹, P. J. MCMILLAN², N. E. HENDRICKS³, J. M. WHEELER⁴, R. L. KOW⁵, N. LIACHKO⁶, B. C. KRAEMER⁷;

¹Div. of Gerontology and Geriatric Med., ²Dept Psychiatry & Behavioral Sci., Univ. of Washington, Seattle, WA; ³SIBCR, ⁴SIBCR, Seattle, WA; ⁵Geriatrics Res. Educ. and Clin. Ctr., Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA; ⁶VA Puget Sound Hlth. Care Syst., Seattle, WA; ⁷GRECC, Univ. of Washington Sch. of Med., Seattle, WA

Abstract: The pathological aggregation of the microtubule-binding protein tau is closely associated with cognitive decline in Alzheimer's disease. We previously identified the E3 ubiquitin ligase adaptor SPOP as a novel genetic contributor to the development of tau toxicity in a *C. elegans* model of human tauopathy. Here, we show that partial genetic depletion of the endogenous mouse SPOP is sufficient to reduce tau aggregation, neuron loss in the CA1 and CA3 regions of the hippocampus, and memory deficits on a Barnes maze task in PS19 mice which express an aggregate-prone human tau mutant (P301S). Deletion analysis of the functional domains of the well-conserved SPOP *C. elegans* homolog *spop-1* suggests its function in the ubiquitin proteasome system (UPS) is necessary for tau toxicity. We specifically identify a putative SPOP substrate, a transcription co-factor, as genetically necessary for *spop-1* suppression of tauopathy in *C. elegans*. RNA sequencing-based transcription factor network analysis in both *C. elegans* and mice nominate several transcription factors linked to SPOP or this substrate with increased estimated activity, highlighting additional and downstream transcriptional mechanisms related to SPOP activity. SPOP's E3 ligase, Cullin3, is upregulated in the frontal cortex of Alzheimer's disease patients compared to age-matched controls, suggesting the translatable relevance of this pathway to disease. Altogether, our results present the ubiquitin adaptor SPOP as a key molecular contributor to tauopathy.

Disclosures: R. Eck: None. P.J. McMillan: None. N.E. Hendricks: None. J.M. Wheeler: None. R.L. Kow: None. N. Liachko: None. B.C. Kraemer: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.11/E36

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: FIDOH 22A07

Title: Alterations of the UFMylation cascade are a common feature of tauopathies

Authors: T. YAN, M. HECKMAN, M. E. MURRAY, D. W. DICKSON, W. SPRINGER, *F. C. FIESEL;
Mayo Clin., Jacksonville, FL

Abstract: Background UFM1 is a small ubiquitin-like modifier that is attached to the lysine residues of substrate proteins, analogous to ubiquitin. Strikingly, UFM1 itself as well as several enzymes involved in the conjugation of UFM1 (UFMylation) have been recently identified as

major modifiers of tau aggregation in two cell-based screens. In human brain, we found distinct alterations in the UFM1 cascade between cases without and with Alzheimer's disease (AD) pathology. Here we expand our analysis of the UFM1 cascade to other neurodegenerative disease conditions to determine whether the identified alterations are specific to tauopathies. **Methods** We have developed and validated novel immunoassays to assess the levels of total UFM1 and UFSP2 and have used these to assess the UFM1 cascade in controls (n=41) and AD (n=72). In order to test the specificity of our findings for tauopathies, we measured UFM1 and UFSP2 in frontal cortex samples from corticobasal degeneration and compared to neurologically normal controls. We also included cases with frontotemporal dementia characterized by TDP-43 pathology and with diffuse Lewy Body disease, characterized by widespread α -synuclein pathology, as additional non-tauopathy controls (n=20 each). Neuropathological measures were assessed by ELISA to perform correlations with UFM1 and UFSP2. In addition, we assessed UFM1 by immunofluorescence and immunohistochemistry staining in brain. **Results** In human AD brain, we found increased levels of total UFM1 and a solubility shift of UFSP2 compared to controls. These molecular changes were specifically correlated with pathological tau, but not with other neuropathological markers. Consistent with a tauopathy-specific pattern, we also detected increased total UFM1 in corticobasal degeneration, but not in frontotemporal dementia or Lewy Body dementia. In the cerebellum of individuals with AD, a region that is unaffected by tau pathology, UFM1 and UFSP2 were also unchanged. In the hippocampus of AD cases, we further confirmed elevated levels of neuronal UFM1 signal by immunohistochemistry and immunofluorescence stainings. **Conclusions** We identified marked changes in the UFMylation pathway in human AD brain and in CBD but not in other neurodegenerative diseases. These changes are significantly associated with pathological tau, suggesting that they are a shared characteristic of tauopathies. Our findings support a modulatory role for the UFM1 cascade in tau pathogenesis within the human brain and underscore the potential of targeting the UFM1 pathway as a promising therapeutic strategy.

Disclosures: T. Yan: None. M. Heckman: None. M.E. Murray: None. D.W. Dickson: None. W. Springer: None. F.C. Fiesel: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.12/E37

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant R01AG084552-01A1
NIH Grant R01NS064131

Title: Examining the effects of sut-6 (NIPP1) mutations on tau or TDP-43-induced toxicity in transgenic *Caenorhabditis elegans* models

Authors: A. SCIOCCHETTI¹, A. BEALE⁶, M. GOLDBERG⁶, R. ECK^{2,3}, A. SAXTON⁶, B. C. KRAEMER^{6,3,4,5}, ***R. L. KOW**^{6,3};

²Grad. Program in Neurosci., ³Div. of Gerontology and Geriatric Med., ⁴Dept. of Psychiatry and Behavioral Sci., ⁵Dept. of Pathology, ¹Univ. of Washington, Seattle, WA; ⁶Geriatrics Res. Educ. and Clin. Ctr., Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA

Abstract: The microtubule-associated protein tau and the DNA/RNA binding protein TDP-43 accumulate pathologically in multiple neurodegenerative diseases including Alzheimer's disease and frontotemporal dementias. Previously we performed forward mutagenesis screening in a transgenic *Caenorhabditis elegans* model of tau pathology, in which human tau protein is overexpressed in all *C. elegans* neurons. We identified a mutation in the gene *sut-6* that suppressed tau or TDP-43-induced locomotor deficits, reduced total tau or TDP-43 accumulation, and reduced neuron loss. The closest human homolog to *sut-6*, NIPP1 (Nuclear Inhibitor of Protein Phosphatase 1), has been shown to bind and modulate Protein Phosphatase 1 (PP1) activity, bind to splicing factors via its forkhead-associated domain, as well as bind to RNA in its C-terminus. The mutation identified in forward mutagenesis, W292X, truncates the last 11 amino acids of the SUT-6 protein, which is predicted to delete part of the RNA binding domain and abrogate RNA binding activity. Here, in addition to the W292X mutation in *sut-6*, we have characterized mutations in either the PP1 binding motif or the predicted forkhead-associated domain. We used co-immunoprecipitation assays to verify that mutation of the PP1 binding motif indeed blocked pull down of the PP1 homolog GSP-1, but that W292X or forkhead-associated domain mutation did not. We then examined whether the PP1 binding mutant could suppress tau or TDP-43 induced behavioral deficits and found no significant effects. We performed similar studies with the forkhead-associated domain mutant. We also examined the effects of these various *sut-6* mutations on splicing using a splicing reporter and observed only small changes. RNA-sequencing of *sut-6*(W292X) and *sut-6*(null) also showed minimal changes to transcription. Our results altogether suggest that *sut-6*(W292X) mutation does not suppress tau or TDP-43 by elimination of PP1 binding or significant alterations to splicing/transcriptional regulation, but by some other mechanism yet to be identified.

Disclosures: A. Sciocchetti: None. A. Beale: None. M. Goldberg: None. R. Eck: None. A. Saxton: None. B.C. Kraemer: None. R.L. Kow: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.13/E38

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: AARF-22-926617

Title: Exploring the link between tau and mitochondria in neurodegeneration

Authors: B. HERNANDEZ¹, J. CRISTOFANO², *J.-H. TSENG²;

¹Neurodegenerative Dis. Res. Ctr., ²Sch. of Life Sci., Arizona State Univ., Tempe, AZ

Abstract: Mitochondrial dysfunction is a hallmark of Alzheimer's disease (AD) and related dementia, yet the mechanisms linking tau pathology to mitochondrial impairment remain unclear. Emerging evidence suggests that tau plays a critical role in regulating mitochondrial function. In this study, we investigated how wild-type tau supports, and disease-associated tau variants compromise, mitochondrial function and neuronal health. We expressed wild-type tau and several disease-relevant tau variants in mammalian cells and primary mouse neurons to evaluate their interaction with mitochondria. Mitochondrial isolation and fluorescence microscopy revealed direct association between tau and mitochondria, with wild-type tau exhibiting greater mitochondrial enrichment than pathogenic variants. Functional assessments demonstrated that cells expressing wild-type tau maintained proper membrane potential, ATP production, and levels of mitochondrial proteins essential for the electron transport chain and mitochondrial dynamics. Moreover, wild-type tau preserved elongated mitochondrial networks, while disease-associated variants led to fragmentation and perinuclear aggregation. These results suggest that wild-type tau supports mitochondrial homeostasis, whereas disease-associated tau variants impair mitochondrial structure and function, contributing to neuronal vulnerability. Targeting these pathological tau species may represent a novel therapeutic strategy for restoring mitochondrial function in AD and related tauopathies. These findings highlight the importance of tau-mitochondria interactions in cellular energy maintenance and suggest that early mitochondrial changes may serve as biomarkers or intervention points in tau-driven neurodegenerative processes.

Disclosures: J. Tseng: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.14/E39

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Alzheimer's Association International Research Grant
Syracuse University Start-up Grant

Title: Restoration of lysosomal acidification via acidic nanoparticles rescues neuronal viability in tauopathies

Authors: *D. T. MURPHY¹, K. KALARY¹, J. ZENG¹, C. LO²;

²Biol., ¹Syracuse Univ., Syracuse, NY

Abstract: Tauopathies, such as Alzheimer's disease (AD), are a group of neurodegenerative diseases marked by the accumulation of tau proteins, resulting in neuronal damage. Tau

aggregates disrupt normal cellular functions, including protein degradation pathways critical for neuronal health. Both cellular and animal studies have linked tau pathology to lysosomal alkalization and impaired autophagy, which exacerbates tau accumulation and further increases toxicity. Correcting lysosomal pH through targeted re-acidification is a promising approach to restore degradation pathways and promote clearance of toxic tau aggregates. In this study, we investigated autolysosomal defects in sporadic models of tauopathies with treatments of tau monomers, oligomers, and fibrils in SH-SY5Y cells. We also characterized autolysosomal impairments in familial models with tauP301S overexpression in SH-SY5Y cells or human induced pluripotent stem cells (iPSCs) neurons carrying tauP301S mutation. We observed that tau species caused degradation defects and metabolic disruptions such as lysosomal alkalization, disrupted autophagic flux, impaired mitochondrial function, resulting in neuronal death. Application of lysosome-targeting acidic nanoparticles (AcNPs) successfully promotes lysosomal acidification, stimulates autophagy, decreases tau accumulation, and alleviates tau-associated neurotoxicity. Together, these results support the therapeutic potential of AcNPs in mitigating tau pathology within cellular models of tauopathies.

Disclosures: D.T. Murphy: None. K. Kalary: None. J. Zeng: None. C. Lo: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.15/E40

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIA Grant R01AG08553
NIA Grant K01AG066747

Title: Delineation of the cellular and molecular drivers of sex- and brain region-specific vulnerability to tau pathology in dementia

Authors: *C. S. CATUMBELA, S. C. HOPP;
UT Hlth. Sci. Ctr. at San Antonio / Glenn Biggs Inst. for Alzheimer's and Neurodegenerativ, San Antonio, TX

Abstract: The cerebral spread of pathological tau protein correlates with the severity of functional decline in neurodegenerative disorders. Such disorders are collectively known as “tauopathies,” including Alzheimer's disease. Notably, there is sex- and brain region-specific vulnerability to tau pathology that remains unexplained. This gap in knowledge critically hinders the development of effective therapeutics against dementia. Intriguingly, due to factors still unclear, the endocytosis of tau fibrils by microglia—the main brain-resident macrophages—can either exacerbate or ameliorate the spread of tau pathology. Perhaps, the propensity of microglia to internalize tau is modulated by cell intrinsic and/or cell extrinsic factors, which may be related

to sex- and brain region-specific differences in microglia themselves or associated cell types. Delineation of sex and regional difference(s) in microglia propensity to internalize tau may unravel associated drivers of vulnerability to tau pathology. To this end, we isolated and cultured adult mouse microglia and non-microglia cells of both sexes from whole brains as well as separate brain regions. We found that microglia from pooled cortical and hippocampal regions exhibit lower tau uptake propensity compared to their counterparts from other brain compartments. However, only the pooled cortical/hippocampal microglia subtype display an increase in tau uptake when treated with media conditioned by associated non-microglia cells (heterogeneous mixture of co-isolated astrocytes and endothelial cells). Strikingly, although media conditioned by whole brain-derived non-microglia cells increased the tau uptake propensity of BV2 cells, a murine microglia cell line, the media required a longer period of conditioning by non-microglia cells from males (48 hours) compared to that by female counterparts (24 hours). Altogether, present data reveal noteworthy sex- and brain region-specific differences in the tau uptake propensity of microglia, which appear to involve cell intrinsic and cell extrinsic modulators. Ongoing efforts include delineation of associated changes to signaling pathways in microglia, in presence and absence of extrinsic factors from homogenous and heterogenous cultures of astrocytes and endothelial cells. Ultimately, this work will contribute to our understanding of sex- and brain region-specific vulnerability to tau pathology and thereby, bridge a consequential knowledge gap.

Disclosures: C.S. Catumbela: None. S.C. Hopp: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Stressmarq, Inc.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.16/E41

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: AG014449
AG072599
AG074004
AG077103
AG085572

Title: Differentiating prodromal stages from progressive degeneration within layer III frontal cortex pyramidal neurons across the Alzheimer's disease spectrum: endosomal-lysosomal and autophagy pathways

Authors: *S. D. GINSBERG^{1,2,3,4}, M. J. ALLDRED^{1,2}, H. PIDIKITI¹, M. MALEK-AHMADI⁵, S. LEE^{1,2}, P. D. COLEMAN⁶, S. CHAKRABARTY⁷, G. CHIOSIS⁷, E. J. MUFSON⁸, G. E. STUTZMANN⁹, A. LABUZA¹;

¹Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; ²Psychiatry, ³Neurosci. & Physiol., ⁴NYU Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; ⁵Banner Alzheimer's Inst., Glendale, AZ; ⁶ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ; ⁷Chem. Biol. and Med., Mem. Sloan Kettering Cancer Ctr., New York, NY; ⁸Translational Neurosci., Barrow Neurolog. Inst., Phoenix, AZ; ⁹Neurosci., Rosalind Franklin Univ. /Chicago Med. Sch., North Chicago, IL

Abstract: Underlying causes of Alzheimer's disease (AD) remain unknown, making it imperative to identify molecular mechanisms driving the pathobiology of AD onset and progression. Laser capture microdissection was employed to isolate layer III pyramidal neurons from postmortem human prefrontal cortex (Brodmann area 9). Single population RNA-sequencing was conducted utilizing tissue from subjects with no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD. DEGs increased from Prodromal (MCI versus NCI) to Progression (AD versus MCI) to Frank AD (AD versus NCI). The majority of DEGs and pathways shared between Prodromal and Progression exhibited a change in the direction of dysregulation unlike pathways between Progression and Frank AD. Specifically, comparison of DEGs obtained from the Prodromal, Progression, and Frank AD were evaluated. A total of 196 DEGs are dysregulated across all clinical groups. The majority of these DEGs are directionally convergent, i.e., upregulated (or downregulated) between Prodromal, Progression, and/or Frank AD, with 95 DEGs convergently upregulated and 40 DEGs convergently downregulated. Prodromal and Progression comparisons frequently observed to have directionally divergent DEGs (e.g., DEGs change direction from upregulation to downregulation or vice versa across cohorts). Directionally divergent DEGs between Progression and Frank AD are also directionally divergent between Prodromal and Progression, indicating unique gene expression alterations in Prodromal compared to Progression and Frank AD. This assessment included DEGs within the endosomal-lysosomal and autophagy pathways. Preliminary evaluation included upregulation of endosomal-lysosomal DEGs during Progression and Frank AD along with downregulation of autophagy pathway DEGs. Moreover, candidate genes and pathways were identified that demarcate early-stage AD onset from AD progression, providing a roadmap to study cortical cellular vulnerability and key targets for intervention at early stages of AD, including endosomal-lysosomal markers and members of the autophagy pathway. We identify distinct changes in gene expression and key bioinformatic pathways from Prodromal, Progression, and Frank AD stages. Genes changed only from NCI to MCI (Prodromal) are prime candidates for early disease biomarkers, whereas genes changed in all 3 conditions are candidates for pan-AD biomarkers. These data can inform future studies of therapeutic targets and highlight the importance of evaluating single populations of vulnerable neurons across the AD spectrum.

Disclosures: S.D. Ginsberg: None. M.J. Alldred: None. H. Pidikiti: None. M. Malek-Ahmadi: None. S. Lee: None. P.D. Coleman: None. S. Chakrabarty: None. G. Chiosis: None. E.J. Mufson: None. G.E. Stutzmann: None. A. Labuza: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.17/E42

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH/NIA R01AG067762
NIH/NIA R01NS082730
Maibach Smiley Endowment

Title: Identification of a novel interaction between tau and NIPSNAP1 mitochondrial protein

Authors: *A. ATWA, N. M. KANAAN;
Translational Neurosci., Michigan State Univ., Grand Rapids, MI

Abstract: Tau is a multifunctional protein that regulates microtubule-dependent and -independent pathways. Abnormal accumulation of misfolded tau is a central pathological feature of neurodegenerative tauopathies, the most common of which is Alzheimer's disease (AD). Among the factors likely contributing to AD progression are mitochondrial dysfunction and impaired removal of damaged mitochondria through mitophagy. Recently, the mitochondrial protein, NIPSNAP1, was identified as a regulator of mitophagy through its accumulation on the outer mitochondrial membrane and facilitating the recruitment of autophagy receptors. Using an unbiased proximity-dependent biotinylation approach (BioID2) coupled with proteomics analysis, we found 324 proteins as potential interactors with tau protein, among which NIPSNAP1 was identified as a candidate tau interactor. In this work, we validated the interaction between tau and NIPSNAP1 using multiple protein-protein interaction assays using postmortem human brain tissue, primary neuronal cultures, and HEK293T cells. Using postmortem human frontal cortex tissue from cognitively unimpaired individuals, co-immunoprecipitation (co-IP) was performed using the Tau13 antibody (total tau) or an IgG1 isotype (control). The amount of NIPSNAP1 that co-IPed with tau was significantly greater than with the control IP (n=5, Mann-Whitney U test). Proximity ligation assays (PLAs) were performed in primary cortical neuron cultures derived from either human tau knock-in (MAPT KI) mice or from tau knockout (Tau KO) mice as a control. PLA using NIPSNAP1 and Tau13 antibodies showed significantly more PLA puncta in MAPT KI neurons when compared to the Tau KO neuron controls (n=4 independent experiments, unpaired Student's t-test). Furthermore, HEK293T cells were co-transfected with plasmids expressing NIPSNAP1 and either full-length 2N4R human tau fused to a Halo tag (ht40-Halo) or Halo-only as a control. The amount of NIPSNAP1 that was pulled down with ht40-Halo was significantly higher than with the Halo-only control (n=4 independent experiments, unpaired Student's t-test). Taken together, the results presented in this work validate the novel interaction between NIPSNAP1 and tau. Future studies will identify the tau domain(s) necessary for this interaction and elucidate the possible function of this interaction in regulating neuronal mitophagy.

Disclosures: A. Atwa: None. N.M. Kanaan: None.

Poster

PSTR017: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR017.18/E43

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Deregulation of a phosphorylation-dependent normal function of tau in mitochondrial reverse electron transport drives tauopathies

Authors: *L. YEUNG;
Pathology, Stanford Univ., Stanford, CA

Abstract: Abstract:

Neurodegenerative diseases, including tauopathies like Alzheimer's disease, are driven by abnormal tau hyperphosphorylation, which leads to the formation of neurofibrillary tangles and ultimately neuronal death. Growing evidence points to mitochondrial dysfunction as a key factor, particularly through tau's interaction with mitochondrial processes. In particular, tau's disruption of mitochondrial dynamics—especially Reverse Electron Transport (RET)—has emerged as a critical driver of disease progression. RET produces reactive oxygen species (ROS) and disrupts the NAD⁺/NADH balance, increasing oxidative stress and damaging mitochondria. In this study, we examine how tau regulates RET and how phosphorylation-related changes in tau affect mitochondrial complex I. Using *Drosophila* models, we find that hyperphosphorylated tau directly activates RET, creating a harmful cycle where tau phosphorylation and RET activation reinforce each other. This feedforward loop amplifies mitochondrial dysfunction and oxidative damage, pushing the neurodegenerative process forward. By targeting hyperphosphorylated tau and inhibiting RET—using both genetic and pharmacological methods—we show that reducing RET significantly lowers pathological tau phosphorylation, decreases ROS levels, and restores NAD⁺/NADH balance. These interventions rescue neuronal function in tauopathy models, reducing neurodegeneration and improving cognitive and behavioral outcomes in *Drosophila*. Further, RET inhibition reduces neuroinflammation and oxidative stress markers, halting the progression of tau-driven cellular damage. Our findings reveal a previously unrecognized role for tau in mitochondrial regulation and suggest that targeting RET offers a specific and promising therapeutic approach. Rather than simply slowing disease progression, this strategy has the potential to reverse neurodegenerative processes in tau-related disorders.

Disclosures: L. Yeung: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.01/E44

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS117906

Title: Impact of short-term e-cigarette exposure on cerebrovascular damage and evaluating the protective role of Metformin: in vitro and in vivo

Authors: *K. AKTER, S. JADHAV, D. MARA, T. J. ABBRUSCATO;
Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX

Abstract: Objectives: Although electronic cigarettes (e-cig) are considered a safer alternative to traditional smoking, the short-term health effects of e-cig remain largely unknown and necessitate thorough research. We hypothesized that short-term exposure to e-cig might result in blood-brain barrier (BBB) disruption and could lead to cerebrovascular toxicities similar to those caused by tobacco smoke (TS) exposure. Previous research suggested that metformin (MF), a first-line antidiabetic drug, effectively prevented the BBB damage associated with TS. Therefore, the current study was designed to investigate the potential role of MF in mitigating e-cig-induced mitochondrial dysfunction and BBB damage, both in vitro and in vivo. We also wanted to evaluate whether there are any gender differences in these cases. **Methods:** We utilized a reliable bEnd3/astrocyte co-culture BBB model to perform permeability studies. Seahorse analysis was conducted on primary neurons and astrocytes after short-term exposure to e-cig w/wo MF treatment. bEnd3 cells were exposed to e-cig w/wo MF treatment, and cell lysates were used for Western blot (WB) analysis of tight junction (TJ) protein expression. CD-1 male and female mice were subjected to a short exposure to e-cig for 7 days, and an open field test was performed. Brain samples were collected from mice and then underwent homogenization and inflammatory cytokines were measured using an immunobead assay. Additionally, brain lysates were analyzed for TJ protein expression through WB. **Results:** Our studies revealed that permeability was increased significantly after acute e-cig exposure and decreased while treated with MF. Additionally, TJ proteins were downregulated both in vitro and in vivo after short-term exposure to e-cig, however, MF upregulates those protein levels. Reduced mitochondrial OCR had been observed after e-cig exposure to neurons and astrocytes and was partially mitigated by MF treatment. Both male and female mice exhibited significant weight loss and hyperactivity after e-cig exposure compared to control mice, but hyperactivity was reduced significantly with MF treatment. Glut-1 but not glut-3 expression was reduced after short-term e-cig exposure, which was further upregulated after MF treatment. Lastly, MF significantly suppressed the release of pro-inflammatory mediators like TNF- α and MCP-1 in male mice but not in female mice. **Conclusion:** These studies support that MF could be an excellent candidate drug for the treatment of e-cig-induced mitochondrial dysfunction and BBB damage and comorbid conditions, like stroke. However, gender roles in responding to MF treatment need further investigation.

Disclosures: K. Akter: None. S. Jadhav: None. D. Mara: None. T.J. Abbruscato: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.02/E45

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Research Foundation of Korea (NRF) Grant
2023R1A2C1004955

Title: Prx4 mitigates glutamate-induced neuronal apoptosis by suppressing ER stress and restoring intracellular redox and calcium balance

Authors: *S. KWON^{1,2}, D. LEE^{1,2};

²Sch. of Life Sciences, BK21 FOUR KNU Creative BioResearch Group, ¹Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: High concentrations of glutamate induce neurotoxicity by eliciting reactive oxygen species (ROS) generation and intracellular Ca²⁺ influx. The disruption of Ca²⁺ homeostasis in the endoplasmic reticulum (ER) evokes ER stress, ultimately resulting in neuronal dysfunction. Additionally, glutamate participates in the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Peroxiredoxins (Prxs) are members of a family of antioxidant enzymes that protect cells from neurotoxic factor-induced apoptosis by scavenging hydrogen peroxide (H₂O₂). Prx4 is located in the ER and controls the redox condition within the ER. The present study investigated the protective effects of Prx4 against glutamate-induced neurotoxicity linked to ER stress. HT22 cells in which Prx4 was either overexpressed or silenced were used to elucidate the protective role of Prx4 against glutamate toxicity. The expression of Prx4 in HT22 cells was significantly increased in response to glutamate treatment, while ROS scavengers and ER chemical chaperones reduced Prx4 levels. Moreover, Prx4 overexpression reduces glutamate-induced apoptosis of HT22 cells by inhibiting ROS formation, Ca²⁺ influx, and ER stress. Therefore, we conclude that Prx4 has protective effects against glutamate-induced HT22 cell damage. Collectively, these results suggest that Prx4 could contribute to the treatment of neuronal disorders.

Disclosures: S. Kwon: None. D. Lee: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.03/E46

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AG039452
Cure Alzheimer's Fund

Title: Molecular signature and functional properties of human pluripotent stem cell-derived brain pericytes

Authors: *M. ZHANG¹, R. RUST¹, A. P. SAGARE¹, Y. KIM¹, K. KISLER¹, C. GRIFFIN¹, Y. WANG¹, V. CLEMENTEL¹, J. TCW², C. TORRES SEPULVEDA¹, B. V. ZLOKOVIC¹, M. P. COBA¹;

¹USC, Los Angeles, CA; ²Boston Univ., Boston, MA

Abstract: Brain pericytes maintain the blood-brain barrier (BBB), secrete neurotrophic factors and clear toxic proteins. Their loss in neurological disorders leads to BBB breakdown, neuronal dysfunction, and cognitive decline. Therefore, cell therapy to replace lost pericytes holds potential to restore impaired cerebrovascular and brain functions. However, the molecular composition and function of human iPSC-derived brain pericytes (iPSC-PC) remains poorly characterized. Here, we show by a quantitative analysis of 8,344 proteins and 20,572 phosphopeptides that iPSC-PC share 96% of total proteins and 98% of protein phosphorylation sites with primary human brain pericytes. This includes cell adhesion and tight junction proteins, transcription factors, and different protein kinase families of the human kinome. In pericyte-deficient mice, iPSC-PC home to host brain capillaries to form hybrid human-mouse microvessels with ligand-receptor associations. They repair BBB leaks and protect against neuron loss, which we show requires PDGFRB and pleiotrophin. They also clear Alzheimer's amyloid- β and tau neurotoxins via lipoprotein receptor LRP1. Thus, iPSC-PC may have potential as a replacement therapy for pericyte-deficient neurological disorders.

Disclosures: M. Zhang: None. R. Rust: None. A.P. Sagare: None. Y. Kim: None. K. Kisler: None. C. Griffin: None. Y. Wang: None. V. Clementel: None. J. Tcw: None. C. Torres Sepulveda: None. B.V. Zlokovic: None. M.P. Coba: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.04/E47

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01DK118082

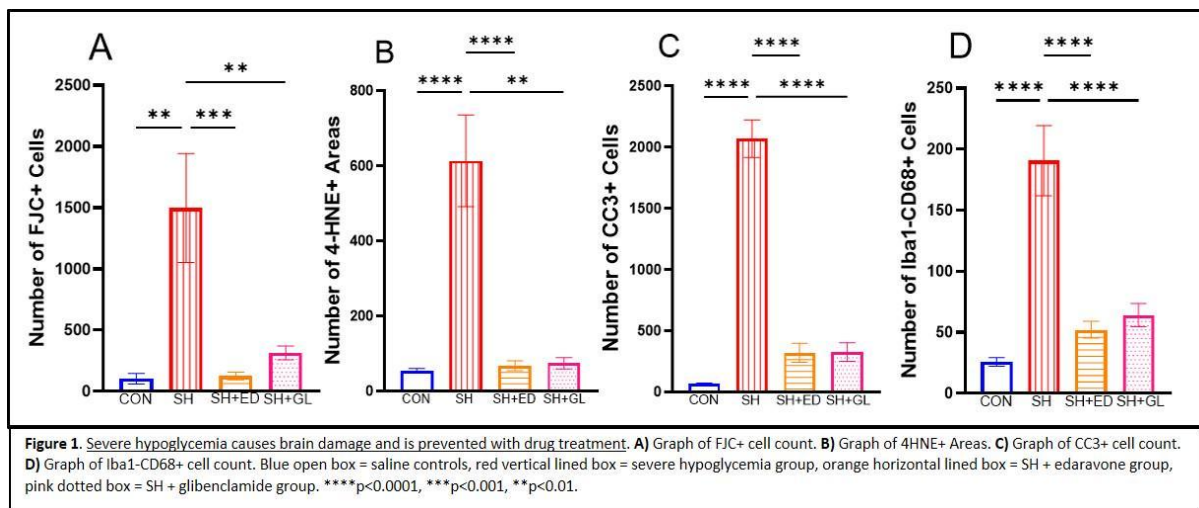
Title: Edaravone and glibenclamide mitigate hippocampal brain damage associated with insulin-induced severe hypoglycemia

Authors: *A. THOMPSON¹, N. PHELPS², H. RILEY², E. BROCKMAN², L. SCHOEDER², M. DEVORE¹, I. PAPAZOGLU², S. J. FISHER³;

¹Pharmacol. and Nutritional Sci., ²Intrnl. Med., ³Intrnl. Medicine; Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: Severe hypoglycemia is a major consequence of intensive insulin therapy in diabetes and is associated with neuronal damage, particularly within the hippocampus. Yet, effective neuroprotective treatments remain elusive. This study investigates whether post-insult administration of two mechanistically distinct neuroprotective drugs—edaravone, a free radical

scavenger, and glibenclamide, an ATP-sensitive potassium channel inhibitor—can attenuate hippocampal injury following insulin-induced severe hypoglycemia. Ten-week-old male Sprague-Dawley rats were assigned to four groups: (1) euglycemic controls, (2) severe hypoglycemia (SH) induced by insulin (15U/kg; blood glucose 10-15 mg/dL for 90 min), (3) SH plus daily for one week with edaravone (3 mg/kg), and (4) SH plus daily with glibenclamide (2.5 mg/kg) (n=5-6/group). One-week post-insult, rats were euthanized, perfused, and 40 μ m coronal sections of the hippocampus were analyzed via immunohistochemistry for markers of cell death (Fluoro-Jade C, Cleaved Caspase-3), neuroinflammation (Iba1/CD68), and oxidative stress (4-Hydroxynonenal). Quantitative analysis was conducted using ImageJ and one-way ANOVA. SH significantly elevated all pathological markers: FJC (10-fold), CC3 (30-fold), Iba1/CD68 (10-fold), and 4HNE (15-fold) compared to controls (all $p < 0.01$). Both edaravone and glibenclamide treatment groups showed significantly reduced expression of all markers, returning to levels not statistically different from controls ($p = \text{NS}$). No significant differences were observed between the two treatment groups. These findings demonstrate that both edaravone and glibenclamide confer robust neuroprotection in the hippocampus following insulin-induced SH. The reduction of cell death, neuroinflammation, and oxidative stress supports their therapeutic potential in mitigating hypoglycemia-related brain injury. This work advances our understanding of neuroprotective treatments in metabolic brain injury and highlights novel pathways for therapeutics in diabetes-related brain damage.



Disclosures: A. Thompson: None. N. Phelps: None. H. Riley: None. E. Brockman: None. L. Schoeder: None. M. Devore: None. I. Papazoglou: None. S.J. Fisher: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.05/E48

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH 1RF1NS127407
Mussallem Transformative Scholar Award

Title: Disruption of Autophagy and Endosomal Pathways Promotes TDP-43 Pathology

Authors: *C. VIETS¹, A. H. HELD², G. ANEX¹, P. SENARATNE², C. MARQUES², S. POWLEY³, M. YATES³, C. LAGIER-TOURENNE³, B. J. WAINGER²;

¹Massachusetts Gen. Hosp., Cambridge, MA; ²Neurol., ³Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Cytoplasmic aggregates of TDP-43 are a pathological hallmark of nearly all amyotrophic lateral sclerosis (ALS) cases, but the mechanisms contributing to their formation and clearance are not fully characterized. We have identified *AP2A1* as a gene that is downregulated in lower motor neurons of sporadic ALS patients, and we have found that knocking down AP2A1 in iPSC-neurons increases cytoplasmic and insoluble TDP-43 and decreases cell survival. AP2A1 belongs to the AP2 complex, and knocking down other AP2 subunits also resulted in increased cytoplasmic and insoluble TDP-43, indicating that AP2A1 regulates TDP-43 through the AP2 complex. AP2 is involved in clathrin-mediated endocytosis and in autophagy through its interactions with clathrin and LC3, respectively. Knocking down LC3, but not clathrin, exacerbated TDP-43 toxicity, suggesting that AP2 regulates TDP-43 primarily through autophagy. Next, using a *Drosophila* model of TDP-43 toxicity, we screened endocytosis and autophagy genes and found that knocking down components of both pathways modified TDP-43 toxicity. Several genes increased neurodegeneration, including Rab5, Rab7, LC3 processing components, phosphatidylinositol kinases, and lysosome fusion proteins. Ongoing studies are validating these hits in iPSC-neurons. We also identified genes that mitigate TDP-43 toxicity, including the previously identified genes *ATXN2* and *PIKFYVE*. Our top suppressor of TDP-43 toxicity is a member of the phosphatidylinositol pathway and mitigates GR dipeptide toxicity, associated with *C9ORF72*-ALS, in both *Drosophila* and iPSC-neuron models. Ongoing studies are now investigating whether this hit improves motor phenotypes and extends survival in mouse models of ALS. These results suggest that the autophagy and endosomal pathways play a critical role in TDP-43 protein homeostasis, and targeting these pathways may present an opportunity for therapeutic intervention.

Disclosures: C. Viets: None. A.H. Held: None. G. Anex: None. P. Senaratne: None. C. Marques: None. S. Powley: None. M. Yates: None. C. Lagier-Tourenne: None. B.J. Wainger: F. Consulting Fees (e.g., advisory boards); QurAlis.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.06/E49

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Research Foundation of Korea (NRF), funded by the Korean government (MSIT) (RS-2023–00218419)
National Research Foundation of Korea (NRF), funded by the Korean government (MSIT) (RS-2024-00335030)
National Research Foundation of Korea (NRF), funded by the Korean government (MSIT) (RS-2022-NR075631)
Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (RS-2025-02303579)

Title: Network Pharmacology-Guided Discovery and Experimental Validation of Natural Pharmaceuticals for Alzheimer's Disease

Authors: M. KIM¹, H.-K. PARK², J.-H. PARK², H.-Y. LEE², S. PARK², Y. YANG⁴, M. KIM⁴, J. SON⁴, J.-H. YANG⁵, J.-H. LEE², W.-Y. LEE⁶, K.-I. PARK⁴, *Y. KIM³;

¹Sch. of Korean Med. Dongguk Univ., Gyeonju, Korea, Republic of; ²Sch. of Korean Med. Dongguk Univ., Gyeongju, Korea, Republic of; ³Sch. of Korean Med. Dongguk Univ., Goyang, Korea, Republic of; ⁴Gyeongsang Natl. Univ., Jinju, Korea, Republic of; ⁵Korea Inst. of Oriental Med., Daegu, Korea, Republic of; ⁶Wonkwang University, Iksan, Korea, Republic of

Abstract: Introduction: Network pharmacology offers a promising framework for elucidating the complex mechanisms of multi-compound natural pharmaceuticals. This study aimed to apply and validate network pharmacology approaches to identify the therapeutic potential and underlying mechanisms of selected natural pharmaceuticals in the treatment of Alzheimer's disease.

Methods: We systematically curated herbal compounds and their targets from five publicly available network pharmacology databases and integrated them into a multiscale protein interactome. Network centrality metrics and path-based algorithms were used to prioritize key targets and predict mechanistic pathways. Experimental validation was conducted using neuronal cells and mice to assess neuroprotective efficacy.

Results: Computational predictions revealed that key neuroprotective mechanisms were mediated through antioxidant and anti-apoptotic pathways. Treatment with selected herbs led to significant improvement in memory performance in the Morris water maze and passive avoidance tests. Histological analyses demonstrated reduced A β accumulation, apoptosis, and neuronal damage. In vitro, neuronal cells showed the decreases in the ROS generation and the restoration of mitochondrial functions. The some bioavailable active compounds in the natural medicine also activated antioxidant signaling, confirming its role as a key neuroprotective agent.

Conclusion: Our findings demonstrate the effectiveness of combining network pharmacology with experimental neuroscience to identify and validate multi-target, natural therapeutic candidates for Alzheimer's disease. This integrative approach provides mechanistic insight into how natural pharmaceuticals exert neuroprotective effects and highlights their potential as complementary treatments for neurodegenerative disorders. *This research was supported by the National Research Foundation of Korea (NRF), funded by the Korean government (MSIT) (RS-2023-00218419, RS-2024-00335030 and RS-2022-NR075631), and also supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (RS-2025-02303579).*

Disclosures: M. Kim: None. H. Park: None. J. Park: None. H. Lee: None. S. park: None. Y. Yang: None. M. Kim: None. J. Son: None. J. Yang: None. J. Lee: None. W. Lee: None. K. Park: None. Y. Kim: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.07/E50

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

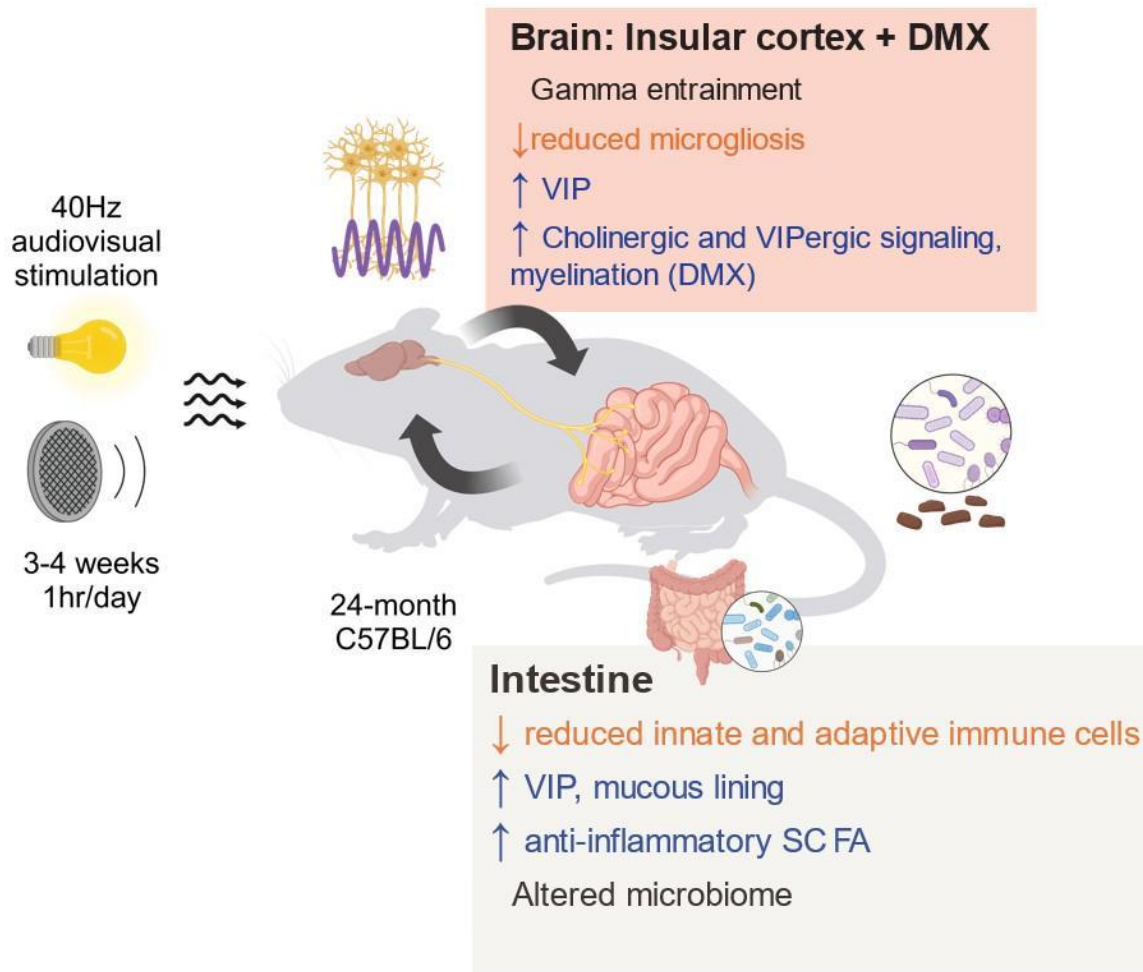
Support: NIH K00 AG073558
NIH R01 AG069232

Title: Regulation of the gut-brain axis via non-invasive gamma sensory stimulation

Authors: N. TAN¹, L. BOZZELLI², *J. PARK³, C.-Y. YANG⁴, E. Y. WANG⁵, K. GUSAROVA⁷, D. EGZIABHER², A. NIU², C. ADAIKKAN⁶, L.-H. TSAI²;

¹Brain and Cognitive Sci., MIT, Boston, MA; ²MIT, Cambridge, MA; ³Brain and Cognitive Sci., MIT, Cambridge, MA; ⁴Basic Med. Sci., MIT, Cambridge, MA; ⁵MIT, Cambridge, MA; ⁶Picower Inst. for Learning and Memory, MIT, Cambridge, MA; ⁷The Picower Inst. for Learning and Memory, Massachusetts Inst. of Technol., Cambridge, MA

Abstract: The gut-brain axis orchestrates complex immune, metabolic, and neuronal interactions, and its dysregulation is increasingly implicated in aging and neurodegenerative disease. While non-invasive gamma-frequency (40 Hz) sensory stimulation—termed Gamma ENtrainment Using Sensory stimulation (GENUS)—has demonstrated neuroprotective effects in the brain, its influence on peripheral systems such as the gut remains unknown. With 24-month-old C57BL/6 wildtype mice, we show that chronic audiovisual GENUS reduces intestinal inflammation, marked by decreases in macrophages, T cells, and innate lymphoid cells. Single-nucleus RNA sequencing revealed transcriptional shifts in enterocytes, including altered expression of defensins—antimicrobial peptides involved in microbial recognition and immune modulation. Fecal analyses demonstrated increased levels of branched short-chain fatty acids (SCFA), microbial metabolites that suppressed inflammatory responses in cultured macrophages. To identify brain regions potentially coordinating these effects, we examined the insular cortex and dorsal motor nucleus of the vagus (DMX)—central hubs of autonomic gut regulation—and found both to exhibit 40 Hz entrainment, increased neuronal activity, and elevated expression of vasoactive intestinal peptide (VIP) and choline acetyltransferase. VIP expression was also increased in neuronal processes within the small intestine, supporting a potential brain-to-gut neuropeptidergic signaling mechanism. Together, these findings position GENUS as a promising, non-invasive approach for enhancing gut-brain health during aging.



Disclosures: N. Tan: None. L. Bozzelli: None. J. Park: None. C. Yang: None. E.Y. Wang: None. K. Gusarova: None. D. Egziabher: None. A. Niu: None. C. Adaikkan: None. L. Tsai: F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.08/E51

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 1R21NS125509-01A1

Title: Neck muscle stimulation accelerates cerebrospinal flow drainage in mice.

Authors: *A. S. REGNIER-GOLANOV¹, E. V. GOLANOV², G. W. BRITZ³;
¹Neurosurg., Houston Methodist Hosp., Houston, TX; ²Neurosurg., The Methodist Hosp., Houston, TX; ³Neurosurg., The Methodist Hosp. - Res. Inst., Houston, TX

Abstract: Cerebrospinal fluid (CSF) has numerous important functional roles. It is thought that CSF plays a critical role providing “sink” for the brain waste products as it exchanges with interstitial fluid during its convective flow through the brain parenchyma, so-called glymphatic flow. Several exit routes for the CSF outflow have been identified: the arachnoid granulations, paravascular and paracranial nerves pathways and meningeal lymphatics. Studies showed that up to 50% of CSF drains through the brain paravenous space, olfactory bulbs and then the cervical lymph nodes. We explored the hypothesis that contraction of the neck muscles, by compressing the underlying cervical valve-equipped lymph vessels and nodes, is capable of accelerating CSF drainage resulting in the accelerated egress of CSF and waste metabolites. In mice (C57BL/6J) we investigated whether electrical stimulation (two subcutaneous needle electrodes are placed 2cm apart on both sides of the neck) is capable of decreasing intracranial pressure (intraventricular pressure sensors), accelerating MRI contrast movement delivered in cisterna magna, resulting in deposition of fluoromicrospheres in the neck lymphatic nodes. We demonstrate that in naive mice, a 5Hz intraburst - 0.1Hz interburst train of bipolar pulses (1 Volt, 1 msec) induced a continuous intracranial pressure (ICP) decrease up to $-41.4\% \pm 6.5$ (mean $\pm$ SD; $P < 0.02$, $n=8$). Analysis of spread of gadolinium MRI contrast revealed accelerated (by $53 \pm 9.4\%$, $P < 0.03$, mean $\pm$ SD; $n=6$) drainage of the contrast from olfactory bulbs after one hour of periodic stimulation. Neck slices immunohistochemistry revealed accumulation of fluoromicrospheres in neck lymphatic vessels immunolabeled with Prox1- lymphatics reporter. We conclude that electromyostimulation of neck muscles in mice accelerates drainage of CSF through olfactory bulb/lymphatic pathways. These observations suggest possible use of neck muscle stimulation to improve CSF outflow and decrease intracranial pressure.

Disclosures: A.S. Regnier-Golanov: None. E.V. Golanov: None. G.W. Britz: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.09/E52

Topic: I.06. Social Cognition

Support: NIH

Title: Meningeal lymphatic restoration improves neurocognitive functions in craniosynostosis

Authors: *Q. CHANG¹, L. MA², J.-F. CHEN³;
¹USC CCMB, Los Angeles, CA; ²USC, Los Angeles, CA; ³Ctr. for Craniofacial Mol. Biol., Univ. of Southern California (USC), Los Angeles, CA

Abstract: The meninges lie in the interface between the skull and brain, harboring lymphatic vasculature and skull progenitor cells (SPCs). How the skull and brain communicate remains largely unknown. We found that impaired meningeal lymphatics and brain perfusion drive neurocognitive defects in Twist1^{+/-} mice, an animal model of craniosynostosis recapitulating human Saethre-Chotzen syndrome. Loss of SPCs leads to skull deformities and elevated intracranial pressure (ICP), while transplanting SPCs back into mutant mice mitigates lymphatic and brain defects through two mechanisms: (i) decreasing elevated ICP by skull correction; and (ii) promoting the growth and migration of lymphatic endothelial cells (LECs) via SPC-secreted vascular endothelial growth factor-C (VEGF-C). Treating Twist1^{+/-} mice with VEGF-C promotes meningeal lymphatic growth and rescues defects in ICP, brain perfusion, and neurocognitive functions. Thus, the skull functionally integrates with the brain via meningeal lymphatics, which is impaired in craniosynostosis and can be restored by SPC-driven lymphatic activation via VEGF-C.

Disclosures: Q. Chang: None. L. Ma: None. J. Chen: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.10/E53

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: R21NS135088

Title: Mesenchymal stem cell derived small extracellular vesicles mediate cerebellar metabolic rescue in sepsis-associated encephalopathy

Authors: D. W. CRAWFORD¹, *M. TRIANTAFYLLOU², N. WOLFF³, P. KRATIMENOS⁴, V. GALLO⁵, I. KOUTROULIS⁶;

¹Seattle Children's Res. Inst., Seattle, WA; ²Children's Natl. Res. Institute, Washington, DC;

³Children's Natl. Res. Inst., Washington, DC; ⁴Neurosci. and Neonatology, Children's Natl. Hospital, George Washington Univ. Sch. of Med. and Hlth. Sci., Washington, DC; ⁵Ctr. for Integrative Brain Res., Seattle Children's Hosp., Seattle, WA; ⁶Emergency Med., Children's Natl. Med. Ctr., Washington, DC

Abstract: Sepsis-associated encephalopathy (SE) is characterized by profound metabolic dysfunction in the brain. In this study, we employed combined targeted and untargeted metabolomics to characterize metabolic alterations in cerebellar tissue and plasma in a murine model of polymicrobial sepsis, with and without treatment using mesenchymal stem cell-derived small extracellular vesicles (MSC-sEVs). Sepsis induced marked cerebellar metabolic derangements, including suppression of oxidative energy metabolism, redox imbalance, and disruption of core amino acid, nucleotide, and TCA cycle pathways. Treatment with MSC-sEVs partially reversed these effects, restoring TCA cycle activity, glutathione balance, and amino

acid metabolism. In contrast, plasma metabolomic profiles showed sepsis-induced alterations but did not significantly differ with MSC-sEV treatment. In contrast, plasma metabolomic profiles reflected disease state but showed minimal treatment-associated changes, suggesting a localized therapeutic effect of MSC-sEVs within the central nervous system. These findings demonstrate that cerebellar metabolomic profiling captures both the impact of sepsis and the metabolic rescue associated with MSC-sEV therapy.<!--EndFragment-->

Disclosures: D.W. Crawford: None. M. Triantafyllou: None. N. Wolff: None. P. Kratimenos: None. V. Gallo: None. I. Koutroulis: None.

Poster

PSTR018: Neuroprotective Mechanisms

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR018.11/E54

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Michael J Fox Foundation Grant: MJFF-022157
Michael J Fox Foundation Grant: MJFF-004005

Title: Selective inhibition of transglutaminase 2 crosslinking activity alleviates α -Synuclein induced phenotype in the mouse preformed fibril model of synucleinopathy

Authors: *K. HASSANZADEH¹, J. LIU², S. MADDILA³, M. MOURADIAN⁴;
¹Rutgers Univ., Piscataway, NJ; ²Neurol., Rutgers - Robert Wood Johnson Med. Sch., Piscataway, NJ; ³Neurol., RWJMS Inst. for Neurolog. Therapeutics, Rutgers Univ., Piscataway, NJ; ⁴Neurol., Rutgers-Robert Wood Johnson Med. Sch., Piscataway, NJ

Abstract: Abstract:

The accumulation of alpha-synuclein (α -Syn) is a central pathological hallmark of synucleinopathies, including Parkinson's disease (PD) and dementia with Lewy bodies (DLB). α -Syn is a known substrate for the crosslinking activity of transglutaminase 2 (TG2) in vitro, in cultured mammalian cells, and in the brains of genetically modified mice. Previously, we demonstrated that overexpression of wild-type TG2 exacerbates the disease phenotype and pathology in synucleinopathy models, whereas TG2 depletion confers protection against α -Syn-induced neurotoxicity. TG2 is a multifunctional enzyme with GTPase, transamidation (crosslinking), protein disulfide isomerase, protein kinase, isopeptidase, and ATPase activities. Our recent work using transgenic mice expressing a catalytically inactive TG2 mutant (W241A) confirms that the crosslinking activity of TG2 plays a critical role in promoting α -Syn aggregation and toxicity. These findings support the therapeutic potential of targeting TG2-mediated transamidation to modify disease progression in PD. In this study, we investigated the therapeutic efficacy of a small molecule TG2 inhibitor that selectively targets transamidation activity in the α -Syn preformed fibril (PFF) mouse model of PD. After completing PK and BBB studies, wild-type and TG2-overexpressing mice were placed on a specialized diet containing the

inhibitor at doses of 300 mg/kg/day or 600 mg/kg/day, starting at four weeks of age. At eight weeks of age, mice received stereotaxic injections of either α -Syn PFF or PBS in the right striatum. Behavioral assessments were conducted at three and six months post-injections. TG2-overexpressing mice injected with PFF exhibited significant behavioral deficits at six months compared to their PBS-injected counterparts and compared to wild-type mice challenged with PFF. Notably, mice receiving the inhibitor-containing diet, particularly at the 600 mg/kg/day dose, showed a better disease phenotype relative to those on the control diet. Pharmacokinetic analysis confirmed that the compound was detectable in both plasma and brain tissue, and TG2 enzymatic activity was significantly inhibited in the 600 mg/kg treatment group. Together, these findings provide in vivo evidence that selective inhibition of TG2's crosslinking activity mitigates α -Syn-driven behavioral impairments, reinforcing TG2 inhibition as a viable disease-modifying therapeutic strategy for synucleinopathies such as PD.

Disclosures: K. Hassanzadeh: None. J. Liu: None. S. Maddila: None. M. Mouradian: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.01/E55

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Protective Functions of NHIP in Neuronal Cells under Hypoxia

Authors: *H. YANG¹, T. SALTER-CID², J. HUANG¹, D. YASUI³, J. LASALLE⁴;

¹Med. Microbiology & Immunol., Univ. of California, Davis, Davis, CA; ²Neurosci., UC Davis - Neurosci. Grad. Group, Davis, CA; ³UC Davis, Davis, CA; ; ⁴UC Davis Sch. Med., Davis, CA.

Abstract: Neuronal Hypoxia-Induced Placenta-Associated (NHIP) is an Autism Spectrum Disorder(ASD) risk gene characterized by reduced expression in ASD and elevated expression under hypoxic conditions in human neuronal cells. This study focuses on investigating the protective role of NHIP in neuronal cells under hypoxic conditions. To achieve this, CRISPR KO and CRISPR-off systems were applied to modulate NHIP expression in SH-SY5Y neuronal cells. The edited SH-SY5Y cells were then exposed to controlled hypoxic conditions (1% O₂) for a specified duration. After that, NHIP expression levels were quantified using qPCR and ELISA, while cell proliferation and viability was assessed using the BrdU and MTT assay. Our results indicate that silenced NHIP expression reduced proliferation and viability of SH-SY5Y cells, particularly under hypoxic conditions. These findings highlight the protective role of NHIP in maintaining neuronal cell survival when hypoxia is induced and suggest the therapeutic potential that NHIP may serve for neurodegenerative diseases.

Disclosures: H. Yang: None. T. Salter-Cid: None. J. Huang: None. D. Yasui: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2C Bioscience. J. LaSalle: E. Ownership Interest (stock,

stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2C Bioscience.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.03/E56

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: BBSRC LIDo PhD Funding

Title: Comparison And Development Of Curcumin Derivatives, CNB-001 And J147 Nanoparticles For Neonatal Neurodegeneration In Hypoxia-Ischemia

Authors: *D. BEGUM;

Inst. for Women's Hlth., Univ. Col. London, London, United Kingdom

Abstract: Neonatal hypoxia-ischemia (HI)- where a newborn's brain is deprived of oxygen and blood- remains a devastating cause of infant mortality globally. A surprising protector may lie in a golden spice: curcumin, the active compound in turmeric. Reported for its powerful antioxidant and neuroprotective effects, curcumin has shown significant therapeutic efficacy in combating HI damage. Advances such as the synthesis of curcumin derivatives (J147, CNB001) and nanotechnology offer solutions to enhance therapeutic efficacy. Thus, this study aimed to compare the biophysical attributes of derivatives in PEGylated (PEG) nanoparticles (NPs) using laser diffraction analysis and antioxidant assays (ANOVA, Tukey post hoc, $n=3$). Results showed that blank PEG NPs measured 223 ± 0.2 nm with a zeta potential of -21.4 ± 9 mV. CNB001 increased size slightly to 227 ± 0.5 nm and reduced surface charge to -3.1 ± 0.2 mV, while J147 increased size to 262 ± 0.8 nm and made the surface more negative at -42 ± 0.2 mV (CNB001: $p=0.01$; J147: $p=0.008$). Particle size changes were not significant versus PEG alone. CNB001-PEG NPs showed a lower IC50 (14 ± 0.1 $\mu\text{g/mL}$) than J147-PEG (25 ± 0.1 $\mu\text{g/mL}$, $p=0.004$), indicating superior antioxidant activity. Despite lower antioxidant content, J147's stronger negative charge may improve therapeutic potential by reducing aggregation and enhancing membrane interaction. Consequently, in vivo studies were conducted using a neonatal mouse model of HI to evaluate therapeutic efficacy. A dose-response study (4, 8, and 17 $\mu\text{g/g}$ body weight) of curcumin derivatives in dimethyl sulfoxide (DMSO) was performed in C57Bl/6 mice (postnatal day 9, $n=16$, mixed sex). Assessment included histological markers such as cell death marker Terminal Uridine Nick End Labelling (TUNEL) and Nissl (Kruskal-Wallis, Dunn's post hoc). Findings demonstrated that both derivatives significantly reduced tissue loss across brain regions compared to the HI and DMSO groups, with CNB001 being most effective at the intermediate dose and J147 at the highest. At the intermediate dose, total volume loss decreased from 13% (HI) to 2.9% with CNB-001 ($p<0.0001$) and 3.1% with J147 ($p=0.0001$), with CNB001 showing slightly greater efficacy. CNB001 significantly reduced mean TUNEL+ cell counts (8.1 vs. 27.4; $p=0.04$), whereas J147 did not (13.4; $p>0.9$). These results suggest

CNB001 has greater potency and a stronger dose-response, effective at lower doses, while J147 requires higher doses for similar effects. Consistent with antioxidant assays, CNB001 may better preserve tissue and reduce cell death, highlighting its antioxidant role and neuroprotective potential, supporting further investigation for HI.

Disclosures: D. Begum: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.04/E57

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2025-00560220)
Korea Drug Development Fund funded by Ministry of Science and ICT, Ministry of Trade, Industry, and Energy and Ministry of Health and Welfare (RS-2025-02182973)

Title: Therapeutic potential of ZCC1, a novel selective MMP-9 inhibitor, with potent neuroprotective effects in ischemic stroke

Authors: *J. LEE¹, Y.-H. KIM^{1,2}, H. LEE², D. KIM²;

¹Sejong Univ., Seoul, Korea, Republic of; ²Zincure corporation, Seoul, Korea, Republic of

Abstract: Stroke remains a leading cause of death and disability worldwide. Ischemic stroke, accounting for ~85% of cases, is caused by interrupted cerebral blood flow, leading to neuronal injury. Reperfusion after ischemia often exacerbates damage via inflammation and vascular dysfunction. A key pathological feature is blood-brain barrier (BBB) disruption, contributing to edema, immune cell infiltration, and secondary neuronal damage. Matrix metalloproteinase-9 (MMP-9), an enzyme that degrades extracellular matrix components, is rapidly upregulated after stroke and plays a central role in BBB breakdown and neuronal death. Elevated MMP-9 activity strongly correlates with worsened outcomes in stroke models. Although inhibiting MMP-9 is a promising therapeutic strategy, previous broad-spectrum MMP inhibitors failed clinically due to off-target effects and toxicity.

To identify selective MMP-9 inhibitors, we screened over 30 novel compounds using in vitro MMP-9 activity assays, cytotoxicity tests, and zinc-induced neurotoxicity models. ZCC1 emerged as a lead compound with favorable efficacy and safety. Its anti-inflammatory activity was evaluated in LPS-treated mouse cerebral cortical cultures, where ZCC1 significantly suppressed both IL-1 β expression and release, outperforming conventional inhibitors GM6001 and JNJ0966. While TNF- α mRNA was unchanged across treatments, its secretion—mediated by ADAM17—was reduced by GM6001 and JNJ0966, but not by ZCC1. This suggests that ZCC1 acts selectively on MMP-9 without affecting ADAM17, avoiding off-target interference.

In a rat model of permanent middle cerebral artery occlusion (MCAO), ZCC1 (5-25 mg/kg, s.c.) was administered one hour post-occlusion. Infarct volume and neurological outcomes at 18 hours showed dose-dependent neuroprotection. Remarkably, 15 mg/kg dosing remained effective even when delayed up to 3 hours post-occlusion.

In conclusion, ZCC1 is a potent and selective MMP-9 inhibitor with strong neuroprotective and anti-inflammatory effects. These findings support its therapeutic potential in ischemic stroke and other neuroinflammatory conditions.

Disclosures: **J. Lee:** None. **Y. Kim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Zincure Corp. **H. Lee:** A. Employment/Salary (full or part-time): Zincure Corp. **D. Kim:** A. Employment/Salary (full or part-time): Zincure Corp..

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.05/E58

Topic: D.04. Brain Injury and Trauma

Support: MSGC Undergraduate Research Fellowship
Hope College

Title: Acute hypoxic exposure in zebrafish impairs olfaction and neuronal mitochondrial function

Authors: **K. DEMANN**¹, **E. DE KOKER**¹, **L. SANCHEZ**¹, **S. DEWITT**², ***E. CALVO-OCHOA**¹;

¹Hope Col., Holland, MI; ²Univ. of Rochester, Rochester, NY

Abstract: Hypoxia, the lack of sufficient oxygen in tissues, hypoxia, has a deleterious effect on neuronal and brain health and function. Zebrafish is an excellent model to study the impacts of hypoxia on the nervous system due to extensive neuroplasticity and injury-induced cell proliferation and since it is a species considered relatively resistant to hypoxia compared to other taxa. The olfactory system, which serves the sense of smell exhibits a remarkable degree of plasticity and neuronal repair and regeneration. It is formed by the olfactory bulb (OB) and the peripheral olfactory epithelium (OE) composed by olfactory sensory neurons (OSNs). Although the integrity of the olfactory system is crucial for its function, the effects of acute oxygen deprivation in the olfactory system have not been explored yet. Thus, we aimed to study olfactory functional and structural integrity after hypoxic exposure and during recovery. In this work, we exposed adult zebrafish to hypoxic conditions of 0.6-0.8 mg/mL dissolved oxygen (DO) for 15 minutes and then let to recover for 1-day (1dph) or 5-days (5dph) post hypoxia (5 dph). Then, to study olfactory function, we assessed olfactory-mediated responses to cadaverine, an odorant that elicits aversive responses in zebrafish, characterized by freezing and darting. To

assess olfactory system integrity we performed immunohistochemical assays to assess (1) structural degeneration, (2) neuronal activity, and (3) neuroinflammation. We also performed biochemical assays to assess mitochondrial dehydrogenase activity to study mitochondrial function. Lastly, we used metformin, an antioxidant that improves mitochondrial activity, to study whether decreasing reactive oxygen species (ROS) and improving mitochondrial activity counteracts the effects of hypoxia in the olfactory system. As a whole, our results characterize olfactory loss and structural alterations in the olfactory system resulting from hypoxia, allowing insights into hypoxia's impact on olfactory function.

Disclosures: K. DeMann: None. E. De Koker: None. L. Sanchez: None. S. DeWitt: None. E. Calvo-Ochoa: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.06/F1

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: PS1 2025

Title: Palmitoylethanolamide attenuates hypoxia-induced morphological and molecular alterations in HT22 hippocampal neurons via activation of pERK/pCREB signaling pathway

Authors: L. UDOVIN¹, D. HUERTA¹, O. GUIMARÃES ALVES¹, *F. CAPANI²;
¹CAEHCIS-CONICET, CABA, Argentina; ²CAEHCIS/CONICET, Buenos Aires, Argentina

Abstract: Neuronal damage caused by hypoxia-reoxygenation is a key mechanism underlying neurodegenerative and ischemic conditions. The hippocampus is especially susceptible to oxygen deprivation, necessitating therapeutic strategies that protect neuronal structure and preserve intracellular signaling. Palmitoylethanolamide (PEA), an endogenous lipid amide, exhibits anti-inflammatory and neuroprotective properties, yet its impact on hypoxia-induced damage in hippocampal neurons remains poorly defined. In this study, we evaluated the protective effect of PEA in a model of hypoxia-reoxygenation using HT22 murine hippocampal cells. Cells were pretreated with PEA (0.01-10 μ M) for 24 or 48 hours and then exposed to hypoxia (1% O₂, 5% CO₂) for 24 or 48 hours, followed by 24 hours of reoxygenation. Cell viability was assessed by Trypan Blue exclusion. Morphological changes were analyzed using phase-contrast microscopy. Western blot was used to measure ERK1/2 phosphorylation, and immunofluorescence assays evaluated nuclear pCREB, NeuN expression, and F-actin organization. Hypoxia-reoxygenation resulted in marked reductions in viability, along with cytoplasmic retraction, nuclear disorganization, and cytoskeletal disruption. Pretreatment with PEA preserved cell viability and improved morphology across all time points. Molecular analysis revealed restoration of ERK1/2 phosphorylation and nuclear pCREB expression in PEA-treated groups. Furthermore, NeuN nuclear localization and F-actin structure were

maintained, indicating cytoskeletal and phenotypic preservation. Together, these findings suggest that PEA confers significant neuroprotection in hippocampal neurons under hypoxic stress by stabilizing structural features and reactivating pro-survival signaling pathways. This supports its potential as a candidate for therapeutic development in conditions characterized by hypoxic neuronal injury.

Disclosures: L. Udovin: None. D. Huerta: None. O. Guimarães Alves: None. F. Capani: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.07/F2

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: MOST 107-2321-B-010-009-MY3
MOST 107-2811-B-010-010
MOST 110-2811-B-A49A-039 (from Ministry of Science and Technology in Taiwan)
Ministry of Education (MOE), Taiwan
NSTC 113-2811-B-A49A-050 (from National Science and Technology Council in Taiwan)

Title: Calpain mediates proteostasis involving activation of GAP43 to facilitate autolysosome formation in cortical neurons

Authors: *C.-C. HUNG¹, C.-Y. LEE¹, W. CHIEN¹, C.-Y. WANG¹, Y.-J. HUANG¹, C.-H. LIN⁴, *C.-C. HUNG², F.-S. SHIE⁵, C.-C. LIAO³, Y.-H. Y. LEE¹;
¹Physiol., ³Tropical Med., ²Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; ⁴Nursing, Kang-Ning Univ., Taipei, Taiwan; ⁵Ctr. For Neuropsychiatric Research, Natl. Hlth. Res. Inst., Zhunan Town, Taiwan

Abstract: Excitotoxic brain injury leads to intracellular calcium overload and subsequent activation of calpains, a family of proteases that regulate neuronal proteostasis. Growth-associated protein 43 (GAP43) is a PKC-dependent neuroplasticity protein known to stabilize actin filaments and promote axonal elongation; however, its role in autophagy regulation remains unclear. In this study, simultaneous GAP43 serine 41 (S41) dephosphorylation and calpain activation were observed in hypoxic-ischemic neonatal rat brain and cultured cortical neurons exposed to excitotoxicity. Notably, no misfolded protein aggregates were detected under these conditions. To address how brain injury-induced calpain activation regulates GAP43-mediated proteostasis through autophagy, we investigated the interplay between calpain activity and GAP43-mediated regulation of proteostasis and autophagy. Our results show that pharmacological inhibition of calpain with calpeptin induced GAP43 dephosphorylation, protein

aggregation, autophagy activation, and neuronal damage in developing neurons in vivo and in vitro. Enhancing GAP43 phosphorylation at S41, either by expressing the phospho-mimetic mutant GAP43S41D or through pharmacological administration LM22A-4, significantly attenuated calpeptin-induced misfolded protein aggregation. This effect of LM22A-4 was abolished by chloroquine, an inhibitor of lysosome-fusion required autophagic flux. Mechanistically, both LM22A-4 and GAP43S41D promoted autophagic flux by enhancing actin-mediated fusion of lysosomes with autophagosomes in the presence of calpeptin, whereas the dephospho- mimetic GAP43S41A had no such effect. In summary, these findings demonstrated that GAP43, in concert with calpain, regulates brain proteostasis by modulating actin organization to facilitate lysosome-mediated autophagic clearance. This study reveals a previously unknown role for GAP43 in autophagy regulation and suggests that GAP43 may serve as a potential therapeutic target in brain disorders characterized by impaired proteostasis.

Disclosures: C. Hung: None. C. Lee: None. W. Chien: None. C. Wang: None. Y. Huang: None. C. Lin: None. C. Hung: None. F. Shie: None. C. Liao: None. Y.Y. Lee: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.08/F3

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Automated video analysis of skilled motor learning after perinatal hypoxic brain injury and neuromodulation in mice

Authors: *N. DROBYSHEVSKY¹, I. GOUSSAKOV²;

¹Evanston Township High Sch., Evanston, IL; ²Pediatrics, NorthShore Univ. HealthSystems, Chicago, IL

Abstract: Background: Perinatal brain injury due to chronic or acute episodes of hypoxia and hypoxia-ischemia (H-I) is a significant cause of neurodevelopmental abnormalities, including cerebral palsy and motor development delay. The lack of objective and automated analysis tools hampers early diagnostics and treatment evaluation. The goal of this study was to develop and apply machine learning algorithms to facilitate neurobehavioral evaluation in juvenile mice after perinatal brain injury. **Methods.** Perinatal brain injury was induced in C57BL/6 mouse pups with 1) an intermittent hypoxia (IH) regimen consisting of 12 to 20 hypoxic episodes daily of 5% oxygen exposure for 2 min at 37 °C from P3 to P7, and 2) H-I in P9 pups with carotid ligation, followed by 45 min of 8% oxygen exposure. Behavioral tests were conducted between P30 and P50 to assess skilled motor learning. Machine learning tools were applied to detect and quantify wrist adjustments during the pasta-eating test and the number of paw slips in the Murray complex wheel tests for 5 days, as observed in video recordings. **Results.** Supervised machine learning was successfully implemented to make predictions based on labeled data. A set of labeled data was prepared for both behavioral tasks. DeepLabCut was used for the pasta-eating

test to track the position of both wrists and the pasta piece. The number of wrist adjustments was estimated to be 6.2 ± 0.7 in the H-I group and 8.5 ± 0.7 in the H-II group. To detect missteps in the complex wheel test, a SlowFast video classifier was implemented in MATLAB. The rate of accurate positive misstep detection was achieved at 92%. **Conclusion.** This study successfully demonstrates the feasibility and high accuracy of using machine learning algorithms for objective and automated neurobehavioral assessment in juvenile mice, providing valuable tools for future research into perinatal brain injury and therapeutic interventions.

Disclosures: N. Drobyshevsky: None. I. Goussakov: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.09/F4

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Cerebral Irisin and its role in post-stroke neuroinflammation and neurogenesis

Authors: *V. VISCARDI^{1,3}, E. LICASTRO¹, N. DI MURAGLIA^{1,3}, M. D'ONOFRIO¹, A. CICATIELLO², M. DENTICE², G. PIGNATARO¹, O. CUOMO¹;

¹Dept. of Neuroscience, Reproductive and Dent. Sci., ²Dept. of Clin. Med. and Surgery, Univ. of Naples Federico II, Napoli, Italy; ³Sch. of Advanced Studies, Ctr. for Neurosci., Univ. of Camerino, Camerino, Italy

Abstract: Physical exercise is being considered as a novel strategy to improve neurodegenerative disease management owing to the boost of myokine production that can stimulate a wide range of biological processes into the brain. Particularly, Irisin, a circulating myokine derived from the cleavage of the cell membrane protein FNDC5 (Fibronectin Type III Domain-Containing Protein 5), can cross the blood-brain barrier and modulate indirectly the neurogenic process, enhancing Brain Derived Neurotrophic Factor expression. Consequently, this evidence sheds light on the potential role of physical exercise and myokines in facilitating the restoration of brain damage and improving the outcomes following ischemic stroke. In this context, our study aimed to: (1) establish a mild physical exercise protocol able to stimulate, in ischemic mice, FNDC5 expression in muscle tissue, and (2) investigate the role of irisin in the ischemic brain. Interestingly, our results, obtained in *in vitro* and *in vivo* models of brain ischemia, demonstrate that not only FNDC5 is physiologically produced within brain cells, but also that its expression significantly increases following exposure to Oxygen and Glucose Deprivation (OGD) in BV-2 mouse microglial cells, thus supporting the involvement of irisin in post-stroke neuroinflammation. Furthermore, immunohistochemical analysis demonstrated the co-localization of FNDC5 with neural progenitor cell markers within neurogenic niches, as well as their co-localization with Irisin's receptor reinforcing the hypothesis that FNDC5/Irisin may play a role in modulating neurogenesis through both direct and indirect mechanisms. Surprisingly, immunofluorescence analysis revealed the presence of irisin receptors on the

plasmamembrane of microglial cells suggesting an autocrine mechanism that expands the initial hypothesis of a simple paracrine effect. Collectively, these results encourage the development of non-invasive and innovative pharmacological strategies for the treatment of ischemic stroke by stimulating irisin release and irisin-mediated pathways to promote neurogenesis.

Disclosures: V. Viscardi: None. E. Licastro: None. N. Di Muraglia: None. M. d'Onofrio: None. A. Cicatiello: None. M. Dentice: None. G. Pignataro: None. O. Cuomo: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.10/F5

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Raynor Cerebellum Project
NIH Grant K12HD001399

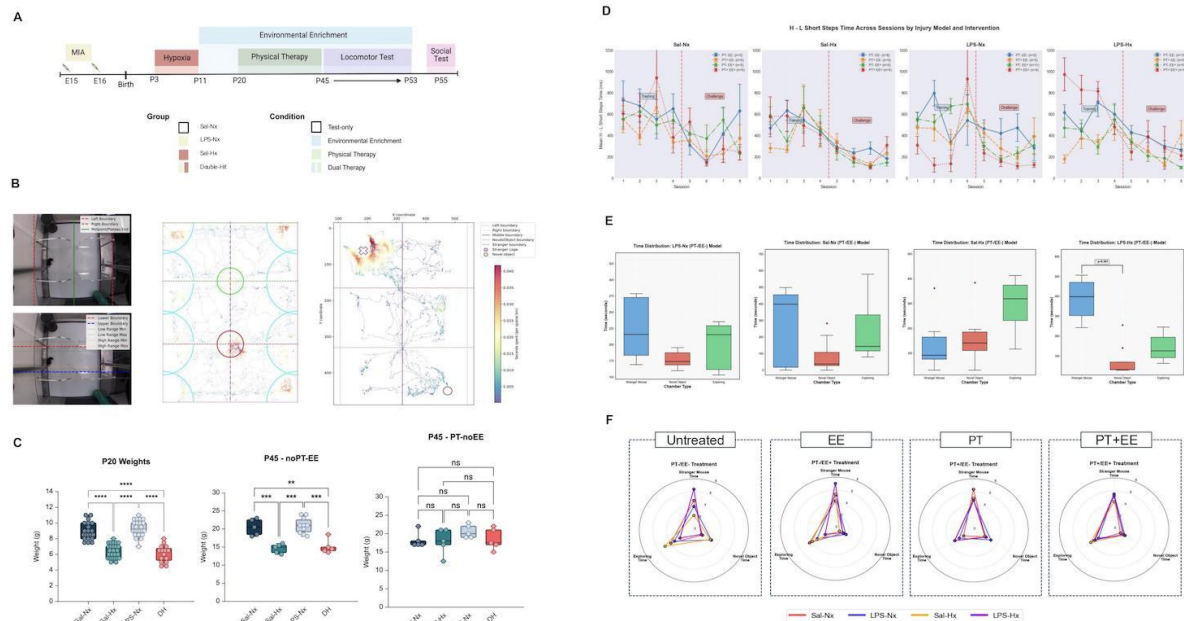
Title: Early postnatal rehabilitation mitigates motor, growth, and social deficits in perinatal brain injury

Authors: *G. SIMONTI¹, R. VIDVA², G. SANIDAS¹, C. BYRD³, C. LOWE¹, M. TRIANTAFYLLOU⁴, N. WOLFF⁶, T. CHANDERENG¹, I. KOUTROULIS⁵, V. GALLO⁷, P. KRATIMENOS⁸;

¹Children's Natl. Hosp., Washington, DC; ²Ctr. of Neurosci. Res., Children's Natl. Hosp., Silver Spring, MD; ³Children's Natl. Res. Inst., Washington, DC; ⁵Emergency Med., ⁴Children's Natl. Med. Ctr., Washington, DC; ⁶Children's Natl. Hosp., Washington DC, DC; ⁷Ctr. for Integrative Brain Res., Seattle Children's Hosp., Seattle, WA; ⁸Neurosci. and Neonatology, Children's Natl. Hospital, George Washington Univ. Sch. of Med. and Hlth. Sci., Washington, DC

Abstract: Early life inflammation and hypoxia, common in preterm birth, disrupt neurodevelopment and elevate the risk for long-term motor, cognitive, and socio-behavioral deficits. While interventions such as physical therapy (PT) and environmental enrichment (EE) offer neuroprotective potential, the injury-specific response to these therapies remains poorly understood. Using a double-hit (DH) mouse model combining maternal immune activation (MIA) and neonatal hypoxia (Hx), we evaluated the efficacy of PT, EE, or combined PT+EE initiated from postnatal day (P) 20 to 45 [F-1A]. Motor learning was assessed via the Erasmus ladder, and social behavior was evaluated using a three-chamber interaction task with a novel proximity index [F-1B]. Untreated Hx and DH mice exhibited persistent weight deficits and impaired motor abilities. Sal-Hx mice showed poor coordination and marked social avoidance, whereas DH mice displayed delayed motor-cognitive responses alongside excessive proximity to the stranger mouse, suggestive of anxiety-driven social attachment. PT alone effectively restored body weight and coordination across all groups, while rescuing motor learning in LPS-exposed mice [F-1CE]. Moreover, PT reversed social avoidance in Sal-Hx mice. EE selectively improved

coordination in Sal-Hx mice but concurrently elicited anxiety-modulated behaviors in all groups, seen as stranger proximity and safety-seeking tendencies, potentially reflecting overstimulation. Notably, the combined PT+EE intervention produced additive benefits in motor outcomes and synergistically normalized social behavior, particularly in DH mice. This resulted in more balanced and normative behavioral phenotypes across experimental groups [F-1F]. PT and EE alone confer domain- and condition-specific benefits following perinatal injury, with dual therapy providing enhanced recovery across motor and socio-behavioral systems. These findings underscore the need for mechanism-based, individualized rehabilitation strategies to optimize neurodevelopmental outcomes in preterm populations.



Disclosures: G. Simonti: None. R. Vidva: None. G. Sanidas: None. C. Byrd: None. C. Lowe: None. M. Triantafyllou: None. N. Wolff: None. T. Chandereng: None. I. Koutroulis: None. V. Gallo: None. P. Kratimenos: None.

Poster

PSTR019: Hypoxia Ischemia

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR019.11/F6

Topic: D.04. Brain Injury and Trauma

Support: TCMMP112-01-03

Title: Decreased P-Selectin Expression in Platelet Function of Stable Neurodegenerative Disease Patients

Authors: *C. SHEN¹, S.-T. TSAI³, Y.-F. WU²;

¹Dept. of Hematology and Oncology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Med. Fndn., Hualien City, Hualien County, Taiwan; ²Dept. of Hematology and Oncology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Med. Fndn., Hualien, Taiwan; ³Neurosurg., Hualien Tzu Chi Hosp., Hualien, Taiwan

Abstract: Platelets are increasingly recognized for their roles in inflammation and neurovascular regulation beyond hemostasis. Altered platelet function has been implicated in neurodegenerative diseases (ND), yet findings remain inconsistent, especially regarding P-selectin (CD62p), a key marker of platelet α -granule secretion and activation. **Objective:** To investigate platelet activation and immune interaction profiles in patients with stable neurodegenerative diseases, with particular focus on P-selectin expression and platelet-leukocyte aggregation. **Methods:** A pilot study was conducted involving patients diagnosed with stable neurodegenerative conditions (without current drug intervention), acute intracerebral hemorrhage (ICH), stable post-ICH, and healthy controls. Platelet function was assessed using flow cytometry with markers including PAC-1 (activated GPIIb/IIIa), CD42b (GPIb), and P-selectin (CD62p). Platelet-leukocyte aggregates were analyzed via surface markers for lymphocytes (CD14, CD33) and myeloid cells. **Results:** Patients with neurodegeneration, acute ICH, and stable ICH exhibited significantly reduced expression of resting platelet markers (CD42b, CD61, CD41) and larger platelet size (increased FSC). PAC-1 expression was preserved in ND patients but reduced in acute and stable ICH. In contrast, P-selectin expression was consistently lower across all patient groups and still decreased even after clinical recovery from brain lesions. Furthermore, lymphocyte-platelet aggregation, particularly with T-lymphocytes, was notably reduced in ND and ICH groups, while myeloid-platelet interaction recovered more quickly in ND and stable ICH cases. **Conclusion:** Our findings reveal persistently impaired platelet activation, characterized by decreased P-selectin expression, in patients with neurodegeneration—distinct from the patterns observed in ICH. The disrupted platelet-lymphocyte interaction suggests an immune modulation component. These results support a link between platelet dysfunction and neurodegenerative pathology, warranting further exploration of platelet-mediated neuroimmune pathways.

Disclosures: C. Shen: None. S. Tsai: None. Y. Wu: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.01/F7

Topic: D.04. Brain Injury and Trauma

Title: Promise and limitations of neuroimaging for detection of CTE-related pathology

Authors: *J. R. CONNOLLY^{1,2}, A. ADAMI³;

¹Psychology, San Diego State Univ., Walnut Creek, CA; ³Psychology, ²San Diego State Univ., San Diego, CA

Abstract: Background: Mild traumatic brain injury (mTBI) is a major public health concern due to its prevalence in contact sports such as American football, soccer, and boxing. Repetitive mTBIs can lead to long-term neurological deficits, including chronic traumatic encephalopathy (CTE), which is typically diagnosed post-mortem or using the traumatic encephalopathy syndrome (TES) criteria in living individuals. Roughly 3.8 million sports-related concussions (SRCs) occur annually in the United States and nearly 50% go undiagnosed or undetected demonstrating a clear and present need for accurate and efficient diagnostic tools for concussions. While cognitive, behavioral, and emotional impairments following concussions are well documented, currently there are no definitive biomarkers that can predict the severity of these impairments. Diffuse axonal injury (DAI) is a crucial pathological finding in both concussions and CTE, that can be detected using diffusion tensor imaging (DTI), an advanced MRI protocol. Fractional anisotropy (FA) and mean diffusivity (MD) values derived from DTI scans which can be used to identify DAI. Preliminary data suggest correlation between DTI variables and behavioral measures (eg, Montreal Cognitive Assessment (MoCA)). The aim of this literature review was to investigate the effectiveness of DTI imaging in identifying chronic symptoms of repetitive mTBI. Methods: Primary research data were gathered using Google Scholar, PubMed, and a general online search with keywords including “DTI”, “MRI”, “Concussion”, and “CTE”. Our initial search criteria yielded 17 primary research articles. However, to ensure data was current and relevant, inclusion criteria limited the review to articles published in 2018 or later that specifically examined DTI techniques. Results: Multiple studies in this review utilized machine learning to identify DTI abnormalities of patients with mTBIs or suffering from post-concussion syndrome (PCS). These findings support the utility of DTI in identifying key traits associated with concussions. Conclusion: DTI analysis shows considerable promise as a tool for detecting white matter abnormalities associated with concussions and CTE, yet it should not be used in isolation. Longitudinal studies integrating neuroimaging with cognitive assessments are needed to validate DTI’s role in CTE identification.

Disclosures: J.R. Connolly: None. A. Adami: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.02/F8

Topic: D.04. Brain Injury and Trauma

Support: Norris Foundation

Title: Grey Matter Volume and Fractional Anisotropy as Correlates of Cognitive Improvement in Traumatic Brain Injury Over a 6-Month Period

Authors: *E. R. ROSARIO, N. FULLMER, C. SCHNAKERS;
Casa Colina Hosp. and Centers for Healthcare, Pomona, CA

Abstract: Objective: To explore how neuroimaging and blood biomarkers relate to cognitive recovery in traumatic brain injury (TBI) patients. Design: Longitudinal observational study. Blood samples, MRI, and diffusion tensor imaging (DTI) were collected at the time of enrollment and again at six months. Additionally, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Disability Rating Scale, and Montreal Cognitive Assessment (MoCA) were administered at both time points to evaluate neuropsychological and functional outcomes. Setting: The study was conducted in a clinical setting, involving participants from an acute rehabilitation hospital. Participants: Sixteen participants with moderate to severe traumatic brain injury (TBI) were enrolled in the study. Interventions: N/A Main Outcome Measures: The primary outcome measures were changes in grey matter volume and fractional anisotropy, as assessed by MRI and diffusion tensor imaging (DTI). Secondary outcome measures included neuropsychological and functional outcomes, evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Disability Rating Scale, and Montreal Cognitive Assessment (MoCA) at both enrollment and six months. Results: Composite RBANS score showed significant change from study enrollment to 6 month follow up ($p = 0.035$). Fractional anisotropy (FA) in the genu ($rs = 0.811$, $p = 0.004$) and splenium of the corpus callosum ($rs = 0.744$, $p = 0.009$) was strongly correlated with changes in the RBANS - Attention index score. Left tapetum FA was correlated with changes in the RBANS - Visuospatial/Constructional index score ($rs = 0.744$, $p = 0.011$). Left temporal fusiform cortex grey matter (GM) volume was correlated with changes in the RBANS - Attention index score ($rs = 0.756$, $p = 0.011$). Blood biomarkers did not show significance. Conclusion: Imaging markers measured at the beginning of the study, such as FA and GM volume, are correlated with 6-month cognitive recovery in TBI, supporting the potential use of neuroimaging to guide rehabilitation strategies.

Disclosures: E.R. Rosario: None. N. Fullmer: None. C. Schnakers: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.03/F9

Topic: D.04. Brain Injury and Trauma

Support: Institute for Collaborative Biotechnologies, Army Research Office Award
Numbers: W911NF-19-2-0026, W911NF-19-D-0001

Title: Detecting recent concussion with multidimensional diffusion imaging: enhanced sensitivity over fractional anisotropy

Authors: *E. RIZOR¹, N. M. DUNDON², S. T. GRAFTON³;

¹Psychological and Brain Sci., UC Santa Barbara, Santa Barbara, CA; ²Psychological & Brain Sci., UCSB, Santa Barbara, CA; ³Psychological & Brain Sci., Univ. of California, Santa Barbara, CA

Abstract: Despite its classification as a “mild” brain injury, concussion causes damaging neural effects not often visually detectable on clinical MRI scans. Concussion-induced white matter (WM) injury can be detected by diffusion imaging using fractional anisotropy (FA). Though FA is interpreted as a marker of “WM integrity”, it cannot distinguish WM microstructural changes from fiber directionality variation. This limitation highlights the need for alternative imaging biomarkers. Multidimensional Diffusion (MDM) imaging provides estimation of “micro” FA (μ FA), which is more robust to fiber directionality variation. Yet, it is unknown whether μ FA and other MDM parameters can reliably detect concussion-related injury. We employed MDM imaging to estimate diffusion markers across WM regions in Concussion (N=30, mean age=21.1, sex=13M/17F, scanned within 5 days of injury) and Control (N=32, mean age=22.8, sex=18M/14F) groups. We assessed: 1) whether regional MDM parameter values are credibly associated with concussion, and 2) whether MDM parameter group discriminability outperforms FA. Lower MDM anisotropy (μ FA, D2anison) and greater MDM isotropy (Diso, Vison; equivalents to mean diffusivity [MD] and MD variance) values were credibly associated with concussion across several regions (94% HDI for β excluded 0). These trends were not unique to areas with crossing fibers. μ FA and D2anison displayed significantly greater discriminability (higher AUC) when compared to FA ($p < 0.001$). MDM parameters, particularly μ FA and D2anison, are promising biomarkers of concussion-induced WM injury. The lack of specificity to crossing fiber areas challenges the idea that axonal shearing drives concussion-induced injury.

Disclosures: E. Rizor: None. N.M. Dundon: None. S.T. Grafton: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.04/F10

Topic: D.04. Brain Injury and Trauma

Support: DOD W81XWH-20-1-0717
NIH 1U24NS140384-01
NIMH R01MH126699
NIBIB R01EB030896
NIBIB R01EB029272
NSF OAC-1916518
NSF IIS-1912270

Title: Clairvoy Revisited: Refining a Diffusion MRI Predictive Model for Concussion Recovery

Authors: S. YI¹, L. ROOKS², G. BERTO⁴, F. PESTILLI⁵, *N. L. PORT³;

¹Indiana Univ., Bloomington, IN; ³Sch. of Optometry, ²Indiana Univ., Bloomington, IN; ⁴Univ. of Texas, Austin, TX; ⁵Psychology, The Univ. of Texas at Austin, Austin, TX

Abstract: Concussion recovery and management remain clinically challenging, particularly in predicting outcomes and identifying cases of prolonged recovery, defined as lasting more than 28 days in collegiate athletes and referred to as persistent post-concussion symptoms (PPCS). Recent studies suggest that diffusion MRI (dMRI) derived metrics, especially fractional anisotropy (FA) and mean diffusivity (MD), combined with tractography-based analyses, can detect white matter microstructural alterations that provide valuable insights into concussion recovery trajectories.

Building on this foundation, we are refining Clairvoy, a predictive model originally developed by Bertó et al. (2024), to enhance its generalizability and usability with new concussion dMRI datasets. Clairvoy is a logistic regression classification model that uses averaged dMRI-derived metrics collected within 24-48 hours post-injury to predict whether a patient will experience recovery lasting longer than 28 days, with an AUC of 0.90.

Our new work focuses on debugging and adapting the original tool to improve its robustness and compatibility across diverse concussion dMRI datasets. Initial validation is underway using a non-NCAA CARE Consortium dataset collected at Indiana University. We plan to extend its application to additional major concussion datasets.

The updated implementation of Clairvoy is designed for integration at the end of dMRI preprocessing pipelines on the open-source, free, and secure reproducible neuroscience analysis platform, brainlife.io, enabling the analysis of microstructural features and offering critical insights into individuals at risk for prolonged recovery.

To our knowledge, this represents the first open-source predictive neuroimaging tool for concussion recovery designed for broad research and potential clinical use. Future work will focus on validating Clairvoy across diverse datasets to further assess its predictive performance and generalizability.

Disclosures: S. Yi: None. L. Rooks: None. G. Berto: None. F. Pestilli: None. N.L. Port: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.05/F11

Topic: D.04. Brain Injury and Trauma

Support: NIH R21
NSF CRCNS US-Japan
Wu Tsai Human Performance Alliance at Stanford University

Title: The Impact of Different Functional Connectivity Measures on the Classification of Harmful Brain Activity Using Various Graph Neural Networks

Authors: *M. ABBASI SISARA¹, M. SALAWAY², M. HAJIAN⁴, F. J. VALERO-CUEVAS³;
¹USC, Los Angeles, CA; ²USC, Scottsdale, AZ; ³Biomed. Engin., USC, La Crescenta, CA;
⁴Univ. of Calabria, Rende, Italy

Abstract: Epilepsy is the second most prevalent neurological disorder, impacting 65 million individuals worldwide. Most epileptic cases (70-80%) can be controlled effectively with antiepileptic medications. In addition to being inaccurate and time-consuming, manually inspecting EEG signals is susceptible to errors. A reliable and accurate automated harmful brain activity classification algorithm based on EEGs would offer a quick and cost-effective solution to a challenging clinical problem. To address this challenge, we develop a graph neural network (GNN)-based framework to classify six patterns of harmful brain activity dataset including: seizure (SZ), generalized periodic discharges (GPD), lateralized periodic discharges (LPD), lateralized rhythmic delta activity (LRDA), generalized rhythmic delta activity (GRDA), or “other”. Considering EEGs as structural time series, they contain separable information about harmful brain activity in terms of time, frequency, and amplitude. We use coherence (in different frequency bands), correlation, and dynamic time warping (DTW) as functional connectivity (FC) of each pair of electrodes, and graph edges are set based on that connectivity. We used graph neural network (GNN), graph isomorphism networks (GIN), and Graph Attention Network (GAT) to leverage functional and structural information of the brain with different FCs. The results indicate that different functional connectivity measures can enhance accuracy, specificity, and sensitivity for various harmful brain activities. By aggregating the best-performing models (GNNs, GINs, and GATs with optimized edge configurations), we achieve the most effective evaluation of harmful brain activity.

Disclosures: M. Abbasi Sisara: None. M. Salaway: None. M. Hajian: None. F.J. Valero-Cuevas: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.06/F12

Topic: D.04. Brain Injury and Trauma

Support: NIH NINDS R21
NSF CRCNS US-Japan
Wu Tsai Human Performance Alliance at Stanford University

Title: The bilateral brain networks for dexterous manipulation are severely compromised by TBI: An identical twins study

Authors: M. ABBASI SISARA¹, S. L. COHEN², M. AZADJOU³, D. DUNCAN⁴, C. LIU¹, *F. J. VALERO-CUEVAS¹;

²Biomed. Engin., ³BME, ¹USC, Los Angeles, CA; ⁴Univ. of Pennsylvania, Los Angeles, CA

Abstract: Objective: To investigate whether axonal shearing during traumatic brain injury affects the bilateral dexterity-dependent networks for dexterous manipulation. Methods: Whole brain functional Magnetic Resonance Imaging (fMRI) on a right-handed traumatic brain injury (TBI) subject and his identical healthy twin compared BOLD signal as they used one hand to compress a slender spring to instability (at 2N of force) vs. a stable wooden dowel (at 1N and 2N) between the thumb and index finger. The spring was compliant but stable when compressed at 1N of force. The tasks were done separately with each hand. Results: As expected, compressing the stable dowel at 1 and 2N produced activity in the contralateral somatosensory cortex; which we also saw with the spring at 1N of compression, albeit with some ipsilateral activity. In contrast, as the compressing of the spring to 2N induced instability, we saw ipsilateral-dominant bilateral brain activity. In the TBI patient, however, all compressions resulted in contralateral brain activity. Conclusions: The dexterity-dependent networks for dexterous manipulation were largely extinguished in this patient with TBI, Significance: This study provides novel insights for evaluating and characterization of the severity of TBI, based on alterations in whole-brain networks and their laterality.

Disclosures: M. Abbasi Sisara: None. S.L. Cohen: None. M. Azadjou: None. D. Duncan: None. C. Liu: None. F.J. Valero-Cuevas: A. Employment/Salary (full or part-time): University of Southern California. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuromuscular Dynamics, LLC.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.07/F13

Topic: D.04. Brain Injury and Trauma

Support: VA Office of Academic Affiliations

Title: Tractometry, a novel pathway forward in identifying differences in mild Traumatic Brain Injury in Veterans

Authors: Y. RAHIMPOUR¹, Y. ZHANG³, M. MOORE⁴, J. W. ASHFORD, Jr.², P. J. BAYLEY⁵, *A. J. FURST³;

¹Stanford Univ., Stanford, CA; ²Stanford Univ., Redwood City, CA; ³VA Palo Alto Hlth. Care Syst., Palo Alto, CA; ⁴VAPAHCS, Palo Alto, CA; ⁵War Related Illness and Injury Study Ctr., VA Palo Alto / Stanford Univ., Palo Alto, CA

Abstract: Background: The goal of this study was to assess the effects of loss (LOC) or no loss of consciousness (nLOC) on white matter integrity in Veterans with Mild Traumatic Brain Injury (mTBI). mTBI is one of the most common types of brain injury and is associated with a wide range of chronic symptoms. To assess the changes that may occur after injury, we used a novel

approach to analyze 100 segments within each of 50 white matter fiber tracts based on diffusion MRI data.

Methods: All data were collected at the War Related Illness and Injury Study Center (WRIISC) at the Veterans Affairs (VA) Hospital in Palo Alto, CA, USA. TBI severity was assessed through self-report questionnaires, clinical reports including diagnosis and screening, and neuropsychological assessments by a WRIISC psychologist. Each participant was identified to either have no TBI or mTBI. 124 Veterans with no TBI and 245 with mTBI were then further divided into nLOC (100) and LOC (145). All Veterans underwent diffusion MRI scans. Pathways were assessed and visualized with FSL and TractSeg. TractSeg is a tool for white matter segmentation in diffusion MRI. Each tract analyzed is assessed along 100 points for significant differences.

Results: A total of 369 (124 no TBI, 100 mTBI nLOC, 124 mTBI LOC) Veterans with a mean age of 55 were analyzed. Significant group differences were observed in several segments of pathways within the two groups of no TBI participants vs. mTBI with nLOC and no TBI vs. mTBI LOC. Multiple comparison corrections are applied using FWE, $p < .0005$. Major differences in each segment were most prominent in Arcuate Fasciculus, Anterior Thalamic Radiation, and the three parts of the Superior Longitudinal Fasciculus.

Conclusion: Several white matter pathways are affected by mTBI. When further differentiating between LOC vs. nLOC, it appears that white matter structures are differentially altered during and/or after time of head trauma. These differences can be utilized for understanding the neuronal damage caused by TBI and provide direction for therapeutic targets of precision medicine.

Disclosures: Y. Rahimpour: None. Y. Zhang: None. M. Moore: None. J.W. Ashford: None. P.J. Bayley: None. A.J. Furst: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.08/F14

Topic: I.04. Executive Functions

Support: Canadian Institutes of Health Research

Title: Longitudinal Changes in Resting-State Network Connectivity and Executive Function Following Moderate-to-Severe Traumatic Brain Injury

Authors: *A. RAHIMIDARABAD¹, A. WASTI^{2,3}, R. GREEN^{2,4,5};

¹Grad. Dept. of Psychological Clin. Sci. (GD-PCS), Univ. of Toronto/University Hlth. Network (UHN), Toronto, ON, Canada; ²Univ. Hlth. Network (UHN), Toronto, ON, Canada; ³Hlth. Sci., Queen's Univ., Kingston, ON, Canada; ⁴Temerty Fac. of Med., Univ. of Toronto, Toronto, ON, Canada; ⁵KITE TeleNeuroRehab Ctr. for ABI, Toronto, ON, Canada

Abstract: Background: Moderate-to-severe traumatic brain injury (msTBI) often results in persistent cognitive impairment and progressive neurobiological changes. Neuroimaging studies have demonstrated declines in brain volume, white matter integrity, and cortical thickness over the months and years following injury. Cognitive outcomes—particularly in executive functions such as working memory and cognitive flexibility—can also deteriorate over time. Emerging evidence suggests that functional brain networks, such as the Default Mode Network (DMN) and Frontoparietal Networks (FPNs), exhibit dynamic changes post-injury, with early increases in connectivity followed by later declines. This pattern may reflect an initial period of adaptive neuroplasticity that supports cognitive recovery, followed by a reduction in network efficiency and maladaptive changes associated with cognitive decline. **Aim:** To determine whether early gains in DMN and FPN connectivity reflect adaptive recovery and whether subsequent declines correspond to maladaptive processes. **Methods:** Using data from a longitudinal msTBI cohort (n = 40), this secondary analysis examined changes in resting-state functional connectivity and executive function across two recovery phases: 6-18 months and 18-36+ months post-injury. Pearson partial correlations (controlling for age) were used to assess associations between connectivity and cognitive change scores (Time 2 - Time 1). **Hypotheses:** (1) In Phase 1, increased connectivity would correlate with cognitive gains; in Phase 2, decreased connectivity would align with reduced gains. (2) Changes in signal variability would relate to executive function performance in both phases. **Results:** In Phase 1, increased mean and log-transformed DMN connectivity were associated with improved working memory (Digit Span Backward: $r = .49$, $p = .005$; $r = .41$, $p = .021$), and greater DMN signal variability was positively associated with changes in visual working memory (Visual Span Backward: $r = .35$, $p = .029$). Conversely, increased right FPN variability was negatively associated with changes in cognitive flexibility (TMT-B: $r = -.35$, $p = .039$). In Phase 2, declines in right FPN connectivity and variability were linked to reduced gains in cognitive flexibility (TMT-B: mean: $r = .43$, $p = .053$; variability: $r = .45$, $p = .041$), with similar marginal effects for the left FPN (mean: $r = .43$, $p = .051$; variability: $r = .43$, $p = .052$). **Conclusions:** Functional connectivity dynamics appear to influence long-term executive outcomes following msTBI, with early increases suggesting adaptive recovery and later declines reflecting maladaptive change.

Disclosures: A. Rahimidarabad: None. A. Wasti: None. R. Green: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.09/F15

Topic: D.04. Brain Injury and Trauma

Support: MN Office of Higher Education - Spinal Cord Injury and Traumatic Brain Injury Research Grant Program (#165646)

Title: Identification of Radiologic Predictors for Post-Surgical Recurrence in Chronic Subdural Hematoma using Machine Learning

Authors: *S. CHEONG¹, Y. SHAM², U. SAMADANI³;

¹Dept. of Bioinformatics and Computat. Biol., ²Integrative Biol. and Physiol., Univ. of Minnesota, Minneapolis, MN; ³US Neurosurg. Associates, New York, NY

Abstract: Chronic subdural hematoma (CSDH) is a prevalent neurosurgical condition. While burr hole drainage is the most common treatment, newer minimally invasive techniques such as the Subdural Evacuating Port System (SEPS) have gained traction due to their reduced surgical burden and bedside applicability. However, SEPS has been associated with a higher hematoma recurrence rate. One factor that may influence recurrence is drill location. This study aims to leverage machine learning to identify features predictive of CSDH recurrence and to predict the optimal drilling point to minimize the risk of CSDH recurrence after SEPS procedures. Pre- and post-operative brain CT images from 21 patients with CSDH who underwent SEPS at the VA hospital were annotated with volumetric and morphologic hematoma characteristics. Features included hematoma volume before evacuation, volume difference post-surgery, radiomic texture measures, and centroid and drill site coordinates. Multiple models including logistic regression, support vector machines (SVM), random forest, and extreme gradient boosting (XGBoost) were evaluated on their accuracy in classifying recurrence. To address class imbalance, Synthetic Minority Over-sampling Technique (SMOTE) was employed, and model performance was assessed via 5-fold cross-validation. Feature importance was assessed using Shapely Additive Explanations (SHAP)-style gain values from the XGBoost model. XGBoost outperformed other classification models (AUC=0.79). The most important predictors of recurrence were hematoma volume (higher volumes), pre- vs. post-op volume difference (>100mL), and Z-axis drill coordinate. Setting the classification threshold at 0.2 yields the highest classification accuracy.

This preliminary study demonstrates that CSDH recurrence can be predicted from pre- and post-op CT images using features such as hematoma volume and drill site locations. Machine learning models can be leveraged in the future to create patient-specific surgical plans to predict the optimal drill site location to reduce recurrence risk.

Figure 1. Model Performance (ROC AUC across 5-fold CV)

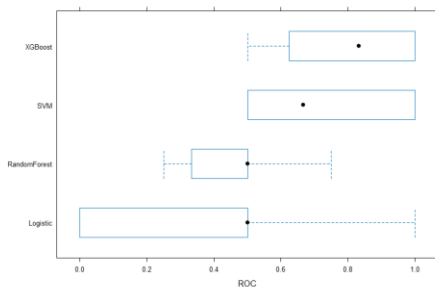


Figure 2. SHAP-style Feature Importance (XGBoost)

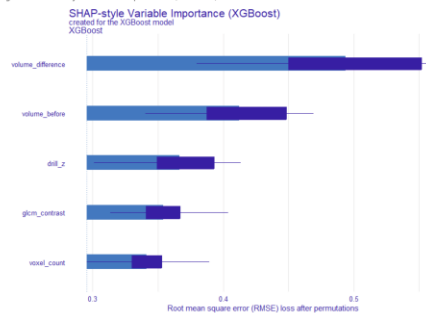


Figure 3. Partial Dependence Plot - Volume Difference

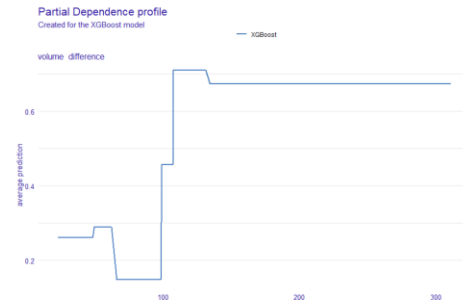
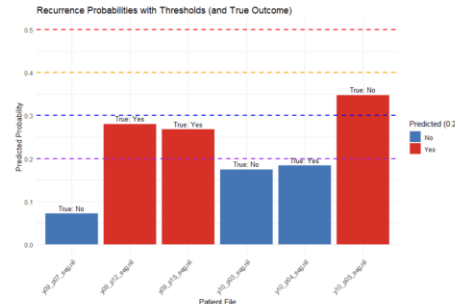


Figure 4. Recurrence Predictions for New Patients (Threshold = 0.2)



Disclosures: S. Cheong: None. Y. Sham: None. U. Samadani: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.10/F16

Topic: D.04. Brain Injury and Trauma

Support: Chaire Fondation Caroline Durand en traumatologie aiguë de l'Université de Montréal
Fonds de recherche du Québec - Programme Audace

Title: Quantifying acute white matter changes during an American football game: A prospective investigation of diffusion MRI and head-impact telemetry data

Authors: *S. GUAY^{1,3}, A. ZAFAR^{3,2}, L. DE BEAUMONT^{2,3};

¹Psychology, ²Univ. de Montréal, Montreal, QC, Canada; ³Sports & Trauma Applied Res. Lab., CIUSSS-NÎM, Montreal, QC, Canada

Abstract: American football raises concerns about brain health from repetitive head impacts, even without traumatic brain injury. While pre-post season white matter (WM) changes have been studied using diffusion MRI (dMRI), limited research exists on acute alterations during a single game with quantifiable impact data and dMRI. This study quantified immediate WM changes in varsity players by comparing pre-post game dMRI-derived metrics with head-impact telemetry.

Thirty-two male football players from three Canadian varsity teams were recruited across two competitive seasons, yielding a 47 distinct game assessments with paired pre- and post-game multi-shell dMRI scans. Pre-game MRI was acquired within 24 hours of the game, while post-game MRI was completed immediately following the game. Participants wore specialized head-impact sensors throughout each game, capturing common impact-related biomechanical metrics. Whole-brain tractograms were generated using TractoFlow, a state-of-the-art dMRI preprocessing pipeline. BundleSeg automatically extracted major WM bundles that were input to Tractometry Flow to perform along-the-tract profiling. Standard DTI, HARDI, neurite orientation dispersion and density imaging (NODDI) measures were computed along 20 sub-sections of each bundle. A principal component analysis reduced the tract profiles to three biologically interpretable principal components: PC1 (fiber coherence), PC2 (global diffusion), and PC3 (fine-scale tissue structure), together explaining 92.5% of variance. To assess whether pre-post game differences were associated with head impact metrics in a single model, we computed dynamic time warping-based similarity matrices for PC-derived features across all scans, applied similarity network fusion to generate aggregated brain-wide diffusion similarity matrices, and extracted pre-post distances for each participant.

Results showed significant associations between head impact exposure and pre-post changes, particularly for PC2 ($p < 0.001$), where all impact groups showed greater change than the low

impact group. Given PC2's link to global diffusion, including NODDI freewater, these findings may reflect sensitivity to acute neuroinflammatory responses, consistent with previous findings in seasonal studies. This study provides new evidence that dMRI can detect microstructural brain changes immediately following a single game, offering a brain-wide sensitive biomarker for tracking the neural consequences of head impacts. It remains to be investigated how these changes fluctuate throughout a season and whether this translates to an accumulating burden over time.

Disclosures: S. Guay: None. A. Zafar: None. L. De Beaumont: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.11/G1

Topic: D.04. Brain Injury and Trauma

Support: Grant support from the Trauma Research & Combat Casualty Care Collaborative, agreement no. 175196 (Sharma)
Financial support from NIH 5R01NS129934-02 (Ding, Zhang, Cardim, Morales)

Title: Neurovascular coupling in hospitalized patients with traumatic disorders of consciousness - a pilot study

Authors: A. SIVATHARMAN¹, D. CARDIM^{2,3}, R. ZHANG^{3,2}, Z. ARMSTRONG⁵, K. DING², J. MORALES², P. EDMUNDSON⁴, H. LIU⁵, *K. SHARMA²;

¹UT Southwestern Med. Sch., Dallas, TX; ²Neurol., UT Southwestern, Dallas, TX; ³Inst. for Exercise and Envrn. Med., ⁴Trauma Surgery, Texas Hlth. Presbyterian Hosp. Dallas, Dallas, TX; ⁵Bioengineering, Univ. of Texas at Arlington, Arlington, TX

Abstract: Background: Prognostication in disorders of consciousness (DoC) after traumatic brain injury (TBI) relies on neurophysiological tools that quantify neuronal and network-level brain function. However, these approaches overlook the role of cerebral vasculature in DoC. Neurovascular coupling (NVC), the coordination between neural activity and cerebral blood flow, may be disrupted in acute TBI, potentially contributing to impaired consciousness. Objective: To assess the feasibility of non-invasively measuring NVC in acute post-TBI period using resting-state EEG-NIRS wavelet coherence analysis.

Methods: Patients with moderate-to-severe TBI were enrolled from the intensive care units (ICU) of two trauma centers. DoC was defined as the inability to follow commands for ≥ 24 hours post-injury. Resting-state EEG (band-pass filtered 0.5-45 Hz) and bi-frontal continuous-wave near-infrared spectroscopy (NIRS) were recorded simultaneously for 30 minutes between days 3-7 post-injury. Frontal EEG channels (F3, F4) were paired with NIRS-oxyhemoglobin signals, and wavelet-based measures of coherence (coupling strength), gain (response

magnitude), and phase (temporal delay) were calculated using MATLAB, focusing specifically on the 0.02-0.2 Hz frequency band. This frequency band captures low-frequency oscillations associated with resting-state network activity and spontaneous hemodynamic fluctuations in the brain.

Results: Eleven patients (mean age 41 ± 18 years, 18% female) were enrolled in the study, with 8 meeting criteria for DoC. Simultaneous EEG-NIRS recordings ranged from 7 to 35 minutes per session. Group-level averages were coherence = 0.27 ± 0.03 , gain = 2.25 ± 3.30 , and phase = 1.73 ± 0.20 radians.

Conclusion: Simultaneous assessment of the dynamic EEG-NIRS relationship is feasible in ICU settings following TBI and enables noninvasive bedside assessment of neurovascular dynamics. This pilot study establishes a framework for quantifying NVC through wavelet-based EEG-NIRS analysis. Ongoing study will determine whether NVC impairment differentiates patients with and without DoC to develop biomarkers of DoC recovery.

Disclosures: **A. Sivatharman:** None. **D. Cardim:** None. **R. Zhang:** None. **Z. Armstrong:** None. **K. Ding:** None. **J. Morales:** None. **P. Edmundson:** None. **H. Liu:** None. **K. Sharma:** None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.12/G2

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant K23NS136745
American Academy of Neurology Clinical Research Training Scholarship
Neurocritical Care Society Research Training Scholarship

Title: Comparative Analysis of fMRI-based Covert Consciousness Methodologies

Authors: ***Q. WU**¹, **K. NGUYEN**², **C. C. BOIVIN**³, **J. B. WARE**⁴, **J. A. DETRE**⁶, **D. FISCHER**⁵;

¹Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA; ²Neurol., ⁴Radiology, ⁵Dept. of Neurol., ³Hosp. of the Univ. of Pennsylvania, Philadelphia, PA; ⁶Dept. of Neurology, Dept. of Radiology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Accurately assessing covert consciousness in patients with disorders of consciousness (DoC) is critical, as behavioral assessments often fail to detect signs of awareness. The traditional approach to analyzing task-based fMRI for DoC, however, is limited. General linear modeling (GLM), the most common technique, risks false positives and false negatives, particularly at the individual-level. In this study, we compared the GLM approach to two data-driven methods: permutation testing (PT), a non-parametric method that is assumption-free, and independent component analysis (ICA), which is agnostic to controlled conditions. To evaluate

the comparative clinical use of these methods, we collected fMRI data (n=29) with current analyses using 8 healthy controls (HC) and 9 DoC patients (3 later recovered) during three 5-minute tasks: two motor command tasks and one auditory language task. Data were preprocessed using fMRIPrep, analyzed and thresholded ($p < .05$) with: (1) GLM (FSL Feat, $Z = 3.1$ cluster threshold), (2) voxelwise PT (FSL randomise, 1000 iterations), and (3) ICA with time-series correlation. Percentages of suprathreshold voxels were extracted from whole-brain (WB) and task-relevant ROIs with positivity defined as $>0\%$ (binary metrics). Across the three tests, all HC showed WB positivity, and only one patient without motor PT positivity. ROI positivity for HC was similar for both tasks with 2 and 1 subjects (out of 9) without ICA positivity. There was less agreement in patients. Patients' motor GLM, PT, ICA positivity rates were 55.6, 33.3, 88.9%, respectively; language had slightly higher rates in GLM (66.7%) and PT (55.6%), but lower for ICA (66.7%). Correlation analysis showed strong agreement in ROI positivity between GLM and PT ($r's = .84 - .97$, $p < .05$), but no significance with ICA. We calculated activation ratios (%ROI activation relative to %WB activation) to quantify task-based activation unique to ROIs; GLM and PT were highly correlated in both tasks for HC ($r's = .81 - .88$, $p's < .05$) but not for patients. These preliminary findings show GLM and PT similarity, but PT generates a lower positivity rate. For DoC patients, PT captured less ROI positivity. This approach can minimize false positives while underestimating patient ROI activation for linear, task-relevant responses. Lower positivity in the motor task may reflect difficulty with explicit commands versus passive listening. In the absence of a gold standard for DoC, a future aim is to model positivity to predict recovery outcomes. With data collection ongoing, a larger sample will help define optimal analytic strategies and improve neuroimaging-based diagnostics for covert consciousness.

Disclosures: Q. Wu: None. K. Nguyen: None. C.C. Boivin: None. J.B. Ware: None. J.A. Detre: None. D. Fischer: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.13/G3

Topic: D.04. Brain Injury and Trauma

Support: National Social Science Foundation of China [Grant No. 22&ZD299]
Shenzhen University Humanities and Social Sciences High-level
Innovation Team Project for Leading Scholars [Grant No. 24LJXZ02]

Title: Individualized Assessment of Patients with Disorders of Consciousness: The Key Role of Functional Network Connectivity during Speech Perception

Authors: *Q. LUO, S. LU;
Shenzhen Univ., Shenzhen, China

Abstract: Objective Identifying the potential advanced auditory processing activity in patients with disorders of consciousness (DoC) is an important clinical need and a challenge in neuroscience. Although previous studies have made attempts to assess types of DoC (e.g., VS & MCS) based on EEG data related to speech perception, limitations still exist, such as insufficient refinement in patient classification, relatively stringent assessing procedures, and the restriction of speech stimuli. **Method** This study hence utilized an easy-to-operate, subject- and environment-friendly functional near-Infrared spectroscopy (fNIRS) to analyze the neural responses of 27 DoC patients (7 VS, 13 MSC and 7 EMCS) and 24 age-matched controls to different natural auditory stimuli (speech, pure tones, animal vocalizations, and music). Through the extraction of various fNIRS features, we employed machine learning methods including Linear Discriminant Analysis (LDA) and Support Vector Machine (SVM) to detect the most type-sensitive dimensions and further explored the neural patterns among different types of patients. **Result** The classification accuracy of functional connectivity data was higher than that of activation and hemodynamic data in both classifiers. The accuracy reached 74.07% when classifying based on coherence values during speech perception. Moreover, all three groups exhibited the highest number of significant functional connections under the speech perception condition. As the level of consciousness improved, connectivity in the prefrontal regions increased. **Conclusion** The use of fNIRS during speech perception tasks holds great potential as a convenient bedside tool for the personalized diagnosis of patients with DoC.

Disclosures: Q. Luo: None. S. Lu: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.14/G4

Topic: D.04. Brain Injury and Trauma

Support: Trauma Research & Combat Casualty Care Collaborative (TRC4), Grant 175196

Title: Resting-state EEG measures of complexity and temporal dynamics improve early outcome classification after cardiac arrest

Authors: *S. BORRAMEO¹, A. SOLODKIN², S. L. SMALL³, K. SHARMA⁴;

¹Univ. of Houston, Houston, TX; ²Neurosci., Univ. of Texas at Dallas, Richardson, TX;

³Neurosci., Univ. of Texas at Dallas, Dallas, TX; ⁴UT Southwestern, Dallas, TX

Abstract: Current clinical prognostic tools for individuals in coma are imprecise, especially in the intensive care unit when decisions about life-sustaining therapies are time-sensitive. To overcome these limitations, studies demonstrate that resting-state EEG (rsEEG) features - capturing spectral power, network connectivity, and signal complexity - can offer insights into brain function and recovery potential in traumatic brain injury. Further, a novel biophysical

measure—irreversibility, which quantifies the directional asymmetry of information flow—has been proposed as a biomarker of consciousness, with temporal-directionality increasing progressively as responsiveness improves in coma, from deep to light sleep, and during emergence from anesthesia. Although theoretically grounded, irreversibility has not been integrated into multimodal prognostic models for anoxic brain injury. This study evaluates the utility of rsEEG features, both independently and combined with clinical data, in a multimodal algorithm for early outcome classification in comatose cardiac arrest survivors. We retrospectively analyzed EEG data from 71 patients, of whom 16 achieved functional independence at hospital discharge (favorable outcome). We computed rsEEG features capturing frequency-specific spectral power and irreversibility (delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-13 Hz), signal complexity and connectivity (theta and alpha bands), and feature variance across epochs. Group differences were assessed via univariate testing (false discovery rate-corrected, $p < 0.001$). All features were entered into an Extra Trees classifier, evaluated by area under the receiver operating characteristic curve (AUC) and 95% confidence intervals. Patients with unfavorable outcomes showed significantly higher variance in signal complexity (Kolmogorov complexity; $U = 180$, $p = 0.0003$). Despite limited value of univariate comparisons, rsEEG features significantly improved classification in multimodal models. AUCs were 0.67 [0.50-0.84] for clinical data, 0.76 [0.58-0.93] for rsEEG alone, 0.78 [0.69-0.87] for clinical + rsEEG (excluding irreversibility), and 0.79 [0.72-0.86] with all features. Both multimodal models outperformed unimodal models ($p = 0.02$), with no significant difference between them. Incorporating rsEEG features significantly improved early outcome classification compared to clinical variables alone. While individual rsEEG features were not strongly associated, their combined use improved model performance. Irreversibility, however, did not improve classification beyond established rsEEG metrics in this dataset.

Disclosures: **S. Borromeo:** None. **A. Solodkin:** 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.; financial support from the Trauma Research & Combat Casualty Care Collaborative (TRC4), Grant agreement no. 175196. **S.L. Small:** None. **K. Sharma:** 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.; financial support from the Trauma Research & Combat Casualty Care Collaborative (TRC4), Grant agreement no. 175196.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.15/G5

Topic: D.04. Brain Injury and Trauma

Support: Leonard Wood Institute in cooperation with the U.S. Army Research Laboratory (W911NF-14 2-0034)

Title: Changes in Amyloid Beta Deposition after Subconcussive Blasts in Military Personnel: Preliminary Study of Effects on Changes in Cognitive Performance and Cortisol Levels

Authors: *M. MUSICH¹, E. HART¹, B. FERGUSON², J. CASSANI¹, A. SINGH¹, D. Q. BEVERSDORF³;

¹Univ. of Missouri, Columbia, MO; ²Univ. of Missouri Thompson Ctr. For Autism, Columbia, MO; ³Dept Radiol, Neurol, Psychol Sci, DGS of INP, Univ. of Missouri Columbia, Columbia, MO

Abstract: During military training, personnel are often exposed to repeated concussive forces leading to traumatic brain injury (TBI). TBI is linked with amyloid beta (AB) accumulation, cognitive impairment development, and acute stress response after injury. Yet, work examining associations between repetitive TBI with AB deposition, cortisol levels, and cognitive functioning in this setting are limited. This study examined associations between these factors. At a U.S. Army base, middle-aged ($N=9$, $M_{age}=33\pm3.37$) male military blasting to breach buildings instructors completed baseline and ~5-month follow-up study visits, including assessments of salivary cortisol, AB positron emission tomography scans, and a computerized cognitive battery (Automated Neuropsychological Assessment Metric) measuring each cognitive domain mean reaction time (RT) in ms and performance accuracy. Between visits, the total amount of training breacher exposures (blasts, demolition) were recorded. Regression (with simple slopes) analyses examined the interaction between changes in AB [negative (AB-), positive (AB+)] and average total of breacher exposures with change scores (follow-up minus baseline) for cortisol levels and cognitive domains. After breacher trainings, $N=4$ instructors had clinically significant AB deposition. Results showed that for AB+ breacher instructors, greater blast exposures were associated with increased processing speed ($b=-3.29$, $SE=.94$, $p=.02$) and inhibition ($b=-1.69$, $SE=.46$, $p=.01$) RT scores, as well as a trend towards reduced inhibition accuracy scores ($b=-.15$, $SE=.06$, $p=.06$). In AB+ breacher instructors, greater demolition exposures were associated with increased processing speed RT scores ($b=-13.28$, $SE=5.02$, $p=.046$) and in delayed memory accuracy scores ($b=.92$, $SE=.29$, $p=.03$). No significant interactions were observed with changes in cortisol levels ($ps>.05$). Findings suggest changes in AB deposition impact cognitive performance but not cortisol levels. AB+ instructors after breacher training showed greater overall breacher exposures, associated with increased processing speed for simple reaction speed and inhibition, and increased delayed memory accuracy scores, but a trend towards reduced inhibition accuracy. It is possible that hypervigilance may contribute to improved processing speed and AB deposition after breacher exposures, whereas AB deposition after specific breacher exposures may lead to a greater cognitive burden of AB for inhibition performance but not delayed memory. Larger longitudinal prospective studies are warranted to inform potential underlying neural mechanisms relating to this relationship.

Disclosures: M. Musich: None. E. Hart: None. B. Ferguson: None. J. Cassani: None. A. Singh: None. D.Q. Beversdorf: F. Consulting Fees (e.g., advisory boards); Quadrant Biosci, YAMO Pharma, Impel Pharma, Scioto Biosci, Stalicia Biosci.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.16/G6

Topic: D.04. Brain Injury and Trauma

Title: Qualification of Neurofilament Light Chain (NfL) as a Biomarker for Drug-Induced Nervous System Injury

Authors: *T. A. LANZ;
Drug Safety Res. & Develop., Pfizer, Groton, CT

Abstract: Neurofilament light chain (NfL) is a neuron-specific protein integral to the neuronal cytoskeleton, released into cerebrospinal fluid (CSF) and blood upon neuronal damage. Elevated serum or plasma NfL levels have been reported in various neurological diseases and injury states. TransBioLine, an Innovative Medicines Initiative funded project, aims to advance the regulatory qualification of NfL as a safety biomarker for drug-induced nervous system (NS) injury for use in Phase 1 clinical trials. Following fit-for-purpose validation of an NfL assay on the Quanterix SIMOA platform, NfL levels were first evaluated in 40 matched pairs of CSF and serum from subjects with multiple sclerosis (MS) and other neurological disorders. A strong correlation was observed between these compartments ($r > 0.69$). A reference range was then established in normal healthy volunteers NHV, aged 18-65 ($n = 270$). A significant effect of age was detected (estimated 2.36% increase per year). To simplify management of age and other subject-specific factors that impact NfL, a second cohort of NHV ($n = 80$) was recruited with longitudinal sampling every 2 weeks for a total of 3 visits. An upper limit of normal (ULN) fold change from baseline was calculated to be 1.64-fold. The performance of NfL as a serum biomarker was then confirmed in cohorts of subjects with mechanical, disease-associated and drug-induced NS injury. In patients with traumatic brain injury ($n = 25$), NfL levels correlated with severity as measured by Glasgow coma score ($r = -0.583$, $p < 0.01$), and levels were 2.6-fold higher in TBI than in NHV. A cohort of MS patients represented disease-associated NS damage ($n = 20$); NfL levels were approximately 2-fold higher in this cohort compared with NHV. Preclinical drug-induced NS injury was evaluated in rats using 7 NS toxicants and 5 non-NS toxicants. Dose-dependent increases in plasma NfL were observed in all studies with NS injury confirmed by histopathology. Chemotherapy was evaluated to provide data on drug-induced NS injury in humans. Serum samples from 48 subjects with or without Paclitaxel chemotherapy were assayed at baseline and 28-weeks later. The fold change from baseline for each visit was 4.72-fold on average for the chemotherapy group, and 0.99-fold for the control group. Putting the ULN threshold into context with our data and published reports on NfL across a large variety of injury and disease settings, the 1.64-fold threshold is well positioned to discriminate between healthy and NS injury. Altogether, these findings provide a framework for longitudinal monitoring of serum NfL as a biomarker for neuronal damage in multiple contexts of use, including drug-induced injury.

Disclosures: T.A. Lanz: A. Employment/Salary (full or part-time): Pfizer, Inc..

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.17/G7

Topic: D.04. Brain Injury and Trauma

Title: Highly sensitive measurement of BD-Tau, NF-L, GFAP, UCH-L1, p-Tau181, and S100B biomarkers in concussion/mild traumatic brain injury serum

Authors: *A. CHENNA^{1,2}, B. YEE², R. MORELAND³, C. PETROPOULOS², J. W. WINSLOW²;

¹LabCorp, South San Francisco, CA; ²LabCorp-Monogram Biosci., South San Francisco, CA;

³Esoteric Immunoassay/Allergy/Special Coagulation Departments, Labcorp-Esoterix, Burlington, NC

Abstract: Concussions and mild traumatic brain injuries (c/mTBI) occur in an estimated 1.6 to 3.8 million recreational and competitive athletes annually in the U.S. Elevations in central nervous system (CNS) proteins, including brain derived Tau (BD-Tau), Neurofilament light chain (NF-L), Glial fibrillary acidic protein (GFAP), Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCH-L1), and phosphorylated threonine 181-Tau (p-Tau181) as well as astroglial protein S100B in blood and cerebrospinal fluid (CSF) have been linked to c/mTBI, making them promising diagnostic and prognostic biomarkers. Recently, the FDA approved GFAP and UCH-L1 as diagnostic biomarkers for TBI. Characterizing the temporal dynamics and interactions of these biomarkers following c/mTBI could enhance their clinical utility, aiding detection, treatment, and recovery. This study utilized SIMOA® Neurology 4-Plex D and p-Tau181 (Quanterix) and Roche S100B assays to quantify biomarker levels in serum samples from 30 cases of c/mTBI at 1-4 hours and 8-16 hours post-injury, alongside 38 healthy controls. BD-Tau, NF-L, GFAP, UCH-L1, and S100B were significantly elevated at both time points compared to controls ($p < 0.0008$), while increases in p-Tau181 were not significant ($p = 0.310$ at 1-4h; $p = 0.121$ at 8-16h). These changes suggest a rapid and sustained response of these biomarkers following brain injury. The Receiver Operating Characteristic (ROC) curve analysis demonstrated strong discriminatory power for BD-Tau, NF-L, GFAP, and UCH-L1 (AUC = 0.92-0.76), with moderate performance for S100B and p-Tau181 (AUC = 0.79-0.68). Correlation analysis revealed strong associations between BD-Tau and UCH-L1, NF-L, GFAP, and p-Tau181 ($r = 0.47$ - 0.70), whereas S100B correlated only moderately with UCH-L1 ($r = 0.42$). These biomarker relationships may reflect distinct yet interconnected pathophysiological responses in neuronal and astroglial injury. Measurements of BD-Tau, NF-L, GFAP, UCH-L1, p-Tau181, and S100B may improve c/mTBI diagnosis and offer valuable prognostic insights into injury severity, neuroinflammatory responses, and long-term recovery trajectories.

Disclosures: **A. Chenna:** A. Employment/Salary (full or part-time): Labcorp-Monogram Biosciences. **B. Yee:** A. Employment/Salary (full or part-time): Labcorp-Monogram Biosciences. **R. Moreland:** A. Employment/Salary (full or part-time): Labcorp-Esoterix. **C. Petropoulos:** A. Employment/Salary (full or part-time): Labcorp-Monogram Biosciences. **J.W. Winslow:** A. Employment/Salary (full or part-time): Labcorp-Monogram Biosciences.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.18/G8

Topic: D.04. Brain Injury and Trauma

Support: NIH S10OD030346

Title: Uncovering the molecular pathophysiology of chronic subdural hematomas

Authors: *N. RAM, G. THINAKARAN;
Mol. Med., Univ. of South Florida, Tampa, FL

Abstract: Chronic subdural hematomas (cSDH) are among the most common neurosurgical conditions in the United States, and their incidence is rapidly rising. The Veterans Affairs predicts that there will be 60,000 new cases of cSDH each year by 2030. Though there have been improvements in the treatment of symptomatic cSDH, little is known about its pathophysiology. cSDH represents a progressive bleed in the subdural space between the dura and arachnoid mater. These hematomas are characteristically encased by outer and inner membranes that border both the hematoma and the meninges. Outer membranes (OMs) are hypothesized to originate from specialized dura border cells and are implicated in the progressive worsening of the condition as well as its recurrence. This fibrotic tissue is largely composed of loosely and tightly woven collagen fibers. Our objective is to perform robust molecular analysis via spatial biology, and biochemical approaches to characterize the molecular and cellular diversity of cSDH outer membranes. We hypothesize that our study will identify key angiogenic and inflammatory pathways and markers in OMs that correlate with the cSDH clinical presentation across patient samples. We performed histological and immunological staining to characterize the spatial distribution of cells and proteins within the OM tissue, which has not been well described in the literature. Our results reveal large blood vessels along the dura-facing border, acellular and cellular intermediate layers, and densely packed cellular layers along the hematoma-facing surface. Multiple cell types, including endothelial cells, vascular smooth muscle cells, fibroblasts, myofibroblasts, and various leukocytes such as eosinophils, macrophages, and neutrophils, are distributed throughout the OM tissue. Furthermore, region-specific transcriptomic analysis using the Nanostring GeoMx Digital Spatial Profiler is beginning to reveal differentially expressed genes and signaling pathways in the OM. Gene ontology analysis of genes expressed in different regions across the OM indicates complement activation, extracellular matrix organization, immune cell recruitment, cell differentiation, vascular development, collagen binding, integrin binding, and fibronectin binding as key regulatory pathways in the dura-facing, highly vascular regions. Our goal is to create a spatial gene expression atlas of the OM across various cSDH stages to further elucidate the pathophysiology of the condition. Consequently, this work aims to inform diagnostic criteria and advance therapeutic approaches to treat cSDH.

Disclosures: N. Ram: None. G. Thinakaran: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.19/G9

Topic: D.04. Brain Injury and Trauma

Support: National Research Foundation in Korea (PhD Fellowship)

Title: Plasma pTau181 tracks cumulative concussion load and forecasts prefrontal hyperactivation in active elite contact-sport athletes

Authors: *S. AHN, W. SONG;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Repeated sport-related concussions (SRC) are thought to initiate tauopathy that ultimately manifests as chronic traumatic encephalopathy, diagnosable only post-mortem, yet objective monitoring of active athletes is rare. A 26-player pilot study showed plasma phosphorylated tau (pTau181) rose with concussion history. We now replicate and extend those findings with a multimarker panel and functional near-infrared spectroscopy (fNIRS). Under IRB approval we enrolled 76 male contact-sport athletes (rugby, boxing, American football; 23 ± 4 y) and 24 age-matched controls. Athletes were stratified by SRC history (None, Once, Multiple). Venous blood was assayed for pTau181, total-Tau, glial fibrillary acidic protein (GFAP), ubiquitin-C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain (NFL) measured on a Simoa HD-X analyzer (Quanterix), and for interleukin-6 (IL-6), tumor-necrosis-factor- α (TNF- α) and C-reactive protein (CRP) by ELISA on an Infinite 200 Pro plate reader (Tecan). Prefrontal fNIRS was recorded at rest and during 2-back and Stroop tasks. Data met Shapiro-Wilk normality (or nonparametric analysis) and were analyzed with covariate-adjusted generalized linear models, partial correlations and backward multiple regression ($p = 0.05$). Athletes exhibited higher pTau181 (+79 %), UCH-L1 (+45 %), IL-6 (+46 %), TNF- α (+32 %) and lower GFAP (-25 %) than controls (all $p < 0.05$). Within athletes, pTau181 increased step-wise across concussion strata (None < Once < Multiple; $p < 0.05$). Reaction times were slower and latencies longer on Stroop, 2-back and dual-task gait, yet mean fNIRS activation did not differ. Lifetime SRC count correlated with pTau181 ($r = 0.31$, $p = 0.008$), and pTau181 remained the sole independent biomarker of SRC load ($\beta = 0.26$). IL-6 plus total Tau explained 22 % of the variance in pTau181. High-pTau athletes (upper quartile ≥ 28 pg mL⁻¹) showed greater bilateral dorsolateral-prefrontal Δ [HbO] during 2-back than low-pTau peers and controls ($\eta^2 = 0.10$, $p = 0.047$); pTau181 correlated with right ($r = 0.34$) and left ($r = 0.29$) Δ [HbO] after adjustment. Together with our pilot data, these results establish plasma pTau181 as a dose-responsive index of cumulative head impacts that forecasts load-dependent cortical hyper-recruitment long before clinical pathology appears. A brief blood draw coupled with wireless fNIRS yields a low-cost,

field-ready screen for proactive neuro-risk stratification and evidence-based return-to-play decisions—an advance ideally suited for SfN Nanosymposium discourse.

Disclosures: S. Ahn: None. W. Song: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.20/G10

Topic: D.04. Brain Injury and Trauma

Support: NINDS 1K23NS110828

Title: Predictors of worsening cerebral edema after traumatic brain injury

Authors: *H. RADABAUGH¹, K. NING², A. ABDELHAK², A. R. FERGUSON¹, H. HINSON²;

¹Neurolog. Surgery, ²Neurol., Univ. of California, San Francisco, San Francisco, CA

Abstract: Cerebral edema (CE) is a key determinant of poor outcomes after traumatic brain injury (TBI). The presence of CE on the initial head computed tomography (CT) scan after TBI is linked to a tenfold increase in mortality compared to patients without CE. There are no validated biomarkers that reflect the biological mechanisms driving edema or to predict its course. Thus, there is a pressing need for validated biomarkers and dynamic predictive models of CE to inform clinical decision-making in the intensive care unit (ICU). We prospectively identified and enrolled adult patients (age >14 years) into an observational cohort ("PROTIPS") at a single center with moderate or severe TBI (GCS 3-12) and evidence of intracranial hemorrhage on the initial head CT. CE was quantified on this CT as "present" or "absent" by a neuroradiologist. We recorded demographics, injury variables, and hospital course variables from the electronic health record. For the cohort, blood was drawn at the time of admission (within 3 hours of injury), centrifuged, aliquoted for plasma, and immediately stored at -80C. We used a high-throughput protein biomarker discovery platform based on Olink's antibody-based proximity extension assay to measure expression levels of 5400 proteins in these samples. Patients were stratified into two groups determined by the presence of CE on the initial CT scan. Protein levels were residualized to adjust for age, sex, and time to admission and then analyzed in parallel using (1) bootstrapped elastic-net regularization with cross-validation and (2) logistic regression with FDR-correction. Proteins identified by both methods were used alongside clinical variables (Admission GCS, GCS Motor, Pupil Reactivity, Admission Glucose Level, and Admission Alcohol Level) to train and evaluate supervised machine learning classifiers for prediction of worsening CE at 6 hours post-admission. One hundred and twenty-six patients were enrolled, 30% had CE at initial scan (n=38), and n=123 had plasma samples available for proteomic analysis. We identified 12 proteins (NECAB2, HPCAL4, GFAP, CEND1, ELAVL4, GAD2, HOMER1, NECAB1, NEFL, RPH3A, GAD1, SNAP25) as robust biomarkers. A total of

116 patients had follow-up CT scans at 6 hours. Among the classifiers tested for their ability to predict CE worsening (n=36; 31%), random forest achieved the highest accuracy (72%; recall = .43; AUC = 0.72). Logistic regression followed closely with a balanced performance (68%; recall: 0.66; AUC= 0.69). These results suggest that a focused panel of protein biomarkers, when combined with targeted clinical variables, can support the accurate prediction of worsening CE.

Disclosures: H. Radabaugh: None. K. Ning: None. A. Abdelhak: None. A.R. Ferguson: None. H. Hinson: None.

Poster

PSTR020: Brain Injury: Human Imaging and Molecular Characterization

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR020.21/G11

Topic: D.04. Brain Injury and Trauma

Support: The Kenneth T. and Eileen L. Norris Foundation

Title: Linking Genetic Markers to Consciousness Impairment in Severe Brain Injury

Authors: *S. SAKELLARIDI^{1,2}, E. R. ROSARIO³, C. SCHNAKERS²;

¹Casa Colina Hosp., Pomona, CA; ³Res. Inst., ²Casa Colina Hosp. and Centers for Healthcare, Pomona, CA

Abstract: Objective: Severe acquired brain injury (sABI) may result in substantial cognitive and physical impairments associated with disorders of consciousness (DoC). Prior research suggests that the presence of DNA markers, such as brain-derived neurotrophic factor (BDNF), apolipoprotein E4 (ApoE4), and catecholO-methyltransferase (COMT), influence patients' recovery after sABI. However, it is not clear which genomic variations are associated with unfavorable outcome after sABI resulting in prolonged DoC. Hence, this study aimed to investigate the presence of these markers in a small population of prolonged DoC to gather preliminary information on polymorphisms linked to poor outcome following sABI. **Design:** In this prospective cross-sectional study, salivary samples were collected and raw genotype data provided after analyses (i.e., DNA extraction and amplification using Polymerase Chain Reaction, and genotyping using Single Nucleotide Polymorphism microarray). **Setting:** Casa Colina Hospital and Centers for Healthcare. **Participants:** Twenty-five patients (mean age: 43.2 ± 7.54 years, 10 women) classified as being in a DoC (i.e., minimally conscious or vegetative state) based on the Coma Recovery Scale-Revised (CRS-R) were included. Etiologies included traumatic brain injuries (n = 11) and anoxia (n = 14). Time since injury ranged from 1-6 years. **Intervention:** Not applicable. **Main Outcome measures:** BDNF (rs6265), ApoE4 (rs7412 and rs429358), and COMT (rs4680) were investigated to determine presence of specific alleles and their frequency in DoC patients. **Results:** For COMT, 80% of patients had alleles associated with poor outcome (20% with alleles GG and 60% with AG). For BDNF, 48% had alleles associated with poor outcome (8% with alleles TT, 40% with CT). Lastly, only 4 patients (16%) had a C

allele for both polymorphisms rs7412 and rs429358, indicating ApoE4 presence. Almost half of the patients (48%; n=12) had more than one marker for poor outcome (mostly BDNF-GG/AG and COMT-TT/CT). A trend to significance was found for the motor function subscale of the CRS-R ($H = 3.033$, $p = 0.084$); scores were lower in patients with more than one marker. No differences were found regarding age, time since injury, etiology, or gender. **Conclusion:** These preliminary findings suggest that COMT and BDNF are the most frequently detected DNA markers in prolonged DoC patients. COMT is linked to lower dopamine levels in the prefrontal cortex, while BDNF is associated with motor deficits such as altered short-term plasticity and motor learning. Confirming these findings and assessing their potential link to the CRS-R, especially the motor subscores, will require a larger sample size.

Disclosures: S. Sakellaridi: None. E.R. Rosario: None. C. Schnakers: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.01/G12

Topic: E.01. Somatosensation – Pain and Itch

Support: National Science and Technology Innovation 2030 Major Program (2021ZD0204400)
National Natural Science Foundation of China (32221003 & 32430038)
State Key Laboratory of Brain Cognition and Brain-inspired Intelligence Technology (TS202401)
New Cornerstone Science Foundation through the XPLOER PRIZE

Title: Alteration of cellular representation in the central amygdala mediates stress-induced analgesia

Authors: *L. WANG, Y. SUN;

Inst. of Neuroscience, CAS Ctr. for Excellence in Brain Sci. & Intelligence Technology, Chi, Shanghai, China

Abstract: Stress-induced analgesia (SIA) is a crucial component of biological adaptation. The central amygdala (CeA) has been implicated in this process, yet its underlying cellular mechanisms remain elusive. Using microendoscopic calcium imaging in freely behaving Sst-Cre, Crh-Cre and Pkc-Δ-Cre mice, we monitored calcium dynamics of genetically defined CeA neuronal subtypes. We found that a subset of somatostatin-expressing CeA neurons (CeA^{Sst}) selectively encode nociception (~11% of 182 neurons from 5 mice), and that acute stress could suppress their responses to noxious stimuli. Interestingly, this stress-induced suppression in the CeA is selective to the representation of nociception, rather than a general alteration in salience coding. Moreover, as the primary local inhibitory input to CeA^{Sst}, corticotropin-releasing hormone-expressing CeA neurons (CeA^{Crh}) exhibited diverse activation patterns in response to

acute stress. Pharmacogenetic and optogenetic inhibition of CeA^{Crh} during acute stress, but not after, significantly reduced SIA (Two-way ANOVA, $p < 0.05$), indicating the state-dependent role of CeA^{Crh} in modulating nociception. Furthermore, combining retrograde tracing, fiber photometry, and pharmacological manipulation, we identified that CeA-projecting neurons in the dorsal raphe nucleus are persistently activated by stress and mediate SIA through activating 5-HT_{2A} receptors in the CeA. Together, our results revealed the cellular and circuit mechanism underlying the SIA mediated by CeA.

Disclosures: L. Wang: None. Y. Sun: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.02/G13

Topic: E.01. Somatosensation – Pain and Itch

Support: grants 2021ZD0204404

Title: Subtypes of in the parafascicular nucleus mediate the nocifensive behavior switch

Authors: *W. QIUMIAO¹, Y. SUN²;

¹Inst. of neuroscience, Chinese Acad. of Sci., Shang Hai, China; ²Inst. of Neuroscience, CAS, Shanghai, China

Abstract: Animals exhibit diverse nocifensive behaviors in responding to noxious stimuli, and these responses are critical for survival of the animal. The circuit mechanism governing their selection and interplay remains elusive. Here we demonstrate that distinct subclasses of neurons within the parafascicular thalamic nucleus (PF) differentially regulate pain-related behaviors in mice. Using pharmacogenetic inhibition and in vivo calcium imaging, we found that Calb1⁺ PF neurons selectively modulate licking behavior in response to noxious stimuli, such as paw pinch, formalin injection, and burn injury, while Tnc⁺ PF neurons predominantly drive defensive attack behaviors. These behaviors are encoded by largely separate neuronal populations, with minimal overlap in responsiveness, as revealed by single-cell resolution imaging in freely behaving mice. Connectomic profiling further identified divergent projection pathways: Calb1⁺ PF neurons target the primary motor cortex to regulate licking, whereas Tnc⁺ PF neurons project to the posterior substantia innominata and nucleus accumbens to mediate attack responses. Additionally, inhibitory inputs from upstream regions, zona incerta and lateral hypothalamic area modulate the balance between these behaviors. Our findings establish the PF as a critical hub for integrating nociceptive information and orchestrating adaptive behavioral responses to pain through topographically organized, parallel circuits.

Disclosures: W. Qiumiao: None. Y. Sun: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.03/G14

Topic: E.01. Somatosensation – Pain and Itch

Support: Uemura Fund UEMURA-2024-2
KAKENHI Grant-in-Aid for Scientific Research 24K19979

Title: Role of Trigeminal Ganglion-Subnucleus Oralis pathway in Orofacial Neuropathic Pain development

Authors: *Y. IDE^{1,2}, S. HITOMI², K. IWATA², M. SHINODA²;

¹Dept. of Complete Denture Prosthodontics, ²Dept. of Physiol., Nihon Univ. Sch. of Dent., Tokyo, Japan

Abstract: Nociceptive neurons have been reported to exist in the trigeminal spinal subnucleus oralis (Vo) of the trigeminal spinal tract nucleus, suggesting its potential involvement in the development of orofacial neuropathic pain. However, how the Vo neurons are involved in orofacial neuropathic pain development is unknown. In this study, we investigate the role of the trigeminal ganglion (TG)-Vo pathway in the development of orofacial neuropathic pain using a partial infraorbital nerve ligation (PNL) model in rats. One-third of the infraorbital nerve was ligated in the PNL group, the Sham group was defined as the group in which only the infraorbital nerve was clearly defined and no nerve ligation was performed. First, we measured the mechanical head-withdrawal threshold (MHWT) of the whisker pad skin. To evaluate the involvement of Vo in orofacial pain sensitivity in PNL group, we assessed MHWT after Vo lesion in PNL group and also after excitation of TG neurons projecting to Vo (TG-Vo neurons) in naïve rats using optogenetic technique. On day 7 after the PNL or sham treatment, we analyzed the response properties of Vo neurons. Furthermore, we examined the expression changes in calcitonin gene-related peptide (CGRP), transient receptor potential ankyrin 1 (TRPA1), and Isolectin B4 (IB4) in TG-Vo neurons and assessed changes in Ca²⁺ influx into acute dissociated TG neurons following administration of a TRPA1 agonist (AITC) in PNL and sham group. The MHWT was significantly lowered in the PNL group compared to the sham group. This lowering was reversed by lesioning the Vo. Mandatory excitation of TG-Vo neurons using optogenetic technique significantly decreased MHWT. Vo neurons in the PNL group were more neuronal responsive than those in the sham group, and these enhanced responses were attenuated by local administration of a TRPA1 antagonist to the whisker pad region. The relative number of CGRP- and TRPA1-positive TG-Vo neurons significantly increased following PNL. Moreover, the PNL group exhibited substantially greater Ca²⁺ influx in TG-Vo neurons after TRPA1 agonist administration than the sham group. These findings suggest that trigeminal nerve injury induces increased expression of CGRP and TRPA1 in TG-Vo neurons and enhances their neuronal excitability, which contributes to the orofacial neuropathic pain development associated with trigeminal nerve injury.

Disclosures: Y. Ide: None. S. Hitomi: None. K. Iwata: None. M. Shinoda: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.04/G15

Topic: E.01. Somatosensation – Pain and Itch

Support: NRF grant, RS-2021-NR059709
NRF grant, RS-2023-00264409
NRF grant, RS-2024-00441103

Title: Brainstem enkephalinergic neural circuit underlying cold-induced pain relief

Authors: *H. KIM¹, Y. LEE¹, S. OH²;

¹Interdisciplinary Program in Neurosci., Seoul Natl. University, Seoul, Korea, Republic of; ²Sch. of Dent, Seoul Nat'l Univ., Seoul, Korea, Republic of

Abstract: The application of cold or cold-mimicking compounds, such as transient receptor potential melastatin 8 (TRPM8) agonists, to the skin has long been recognized as an effective means of alleviating pain. However, the underlying neural mechanisms have remained largely elusive. In this study, we identified a specific neuronal subset within the lateral parabrachial nucleus (IPBN)—a thermosensory relay center in the hindbrain—as a critical mediator of cold-induced analgesia, through enkephalinergic signaling and descending pain modulation pathways. Utilizing FosTRAP transgenic mice in combination with chemogenetic techniques, we demonstrated that activation of cold-responsive IPBN neurons and their projection to ventrolateral periaqueductal gray (vIPAG) significantly increased hot and mechanical pain threshold. Conversely, ablation of these neurons attenuated the analgesic effect of cold-mimicking chemical, without altering baseline nociceptive response, thermal preference or baseline core body temperature. Neural population-selective sorting and subsequent RNA sequencing analysis revealed that cold-responsive neurons in IPBN express the precursor gene for enkephalin (*penk*; 53% of cold-responsive neurons). Furthermore, activation of these neurons or peripheral exposure to cold stimuli increased enkephalin levels within the vIPAG, implicating an enkephalinergic signaling underlying IPBN-to-vIPAG neural circuit. Supporting these results, local administration of enkephalin-neutralizing antibody or opioid receptor antagonist naloxone to vIPAG effectively abolished cold-mimicking chemical-induced analgesia, highlighting the involvement of endogenous opioid system in cold-induced pain relief. Analgesic cold stimuli activated vIPAG and rostral ventrolateral medulla (RVM), suggesting the engagement of descending pain modulation pathway. In accordance with this, activation of cold-responsive neurons in the IPBN or RVM suppressed noxious mechanical stimuli-induced Fos expression in the lumbar spinal cord (both superficial layer and deep layer), further confirming an involvement of top-down descending pain modulation. Collectively, these findings provide novel insights into the neural circuitry underlying cold-induced analgesia and highlight a pivotal role of the IPBN-to-vIPAG pathway in TRPM8-dependent analgesia, which could be a novel target for pain treatment.

Disclosures: **H. Kim:** None. **Y. Lee:** None. **S. Oh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Seog Bae Oh is a founder of OhLabBio.. Other; Seog Bae Oh is involved in planned patents regarding 'NK cells-based immunotherapy for neuropathic pain'..

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.05/G16

Topic: E.01. Somatosensation – Pain and Itch

Support: CIHR

Title: Decoding the ventrolateral periaqueductal gray (vlPAG) to locus coeruleus (LC) circuit in pain and anxiety regulation

Authors: *J. YU^{1,2}, G. ZAMPONI³;

¹The Hotchkiss Brain Institute, Univ. of Calgary, Calgary, AB, Canada; ²Alberta Children's Hosp., Calgary, AB, Canada; ³Univ. of Calgary, Calgary, AB, Canada

Abstract: Pain can be a debilitating condition, with patients often facing limited treatment options. Therefore, understanding how pain signals are processed in the brain is essential. The periaqueductal gray (PAG) plays a crucial role in the regulation of chronic pain. It receives important input from upstream brain regions such as the medial prefrontal cortex (mPFC), processes this information, and sends outputs to the LC. The LC is the primary source of norepinephrine (NE) and has major projections to the mPFC. Here, I first show how glutamatergic and GABAergic input from the vlPAG to the LC distinctly regulate pain and anxiety under both normal and neuropathic pain conditions. Glutamatergic input appears to provide analgesic and anxiogenic effects, whereas GABAergic input produces an anxiolytic effect without altering pain. Next, when DSP4—a selective neurotoxin that primarily targets the noradrenergic system of the LC—is injected into the mPFC, the previously observed effect on anxiety is abolished, which demonstrates that NE projections to the mPFC play an important role in anxiety regulation. Additionally, we investigated a small population of GABAergic cells located medially to the LC, referred to as the peri-LC. These cells potentially interact and regulate LC activity and may be involved in the vlPAG-LC circuit. Optogenetic activation of the vlPAG GABAergic input to the peri-LC produced both analgesic and slight anxiolytic effects in various behavioral assays. Confocal imaging further revealed that activation of this input robustly increased c-Fos expression in the LC under both control and spared nerve injury (SNI) conditions. This suggests a potential GABA-GABA disinhibition mechanism occurring within the LC. These findings emphasize the importance of understanding the vlPAG-peri-LC-LC pathway in regulating pain and anxiety and may offer new insight for developing strategies to alleviate chronic pain in the future.

Disclosures: J. Yu: None. G. Zamponi: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.06/H1

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NS117899
NIH Grant R01NS135401

Title: Module-selective pharmacological targeting of medial prefrontal cortex-projecting locus coeruleus neurons drives antinociception

Authors: *C.-C. KUO¹, J. G. MCCALL²;

¹Washington Univ. in St. Louis, St. Louis, MO; ²Anesthesiol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Selective manipulation of neural circuits using optogenetics and chemogenetics tool holds great translational potential but constrained by the need of genetic access to neurons. Here, we demonstrate a general framework for identifying genetic tool-independent, pharmacological strategies for neural circuit-selective modulation. As a testbed for this approach, we used the mouse locus coeruleus due to the combination of its widespread, modular efferent neural circuitry and its wide variety of endogenously expressed G-protein coupled receptors. We developed an economically accessible calcium imaging-based approach for large-scale, *ex vivo* pharmacological scans of endogenous receptor-mediated neural activity. Using machine learning-based action potential deconvolution and retrograde tracing, we designed a pharmacological cocktail—comprising agonists targeting mu opioid, 5HT1a and muscarinic-1 receptors—that selectively inhibits medial prefrontal cortex-projecting locus coeruleus neurons. *In vivo*, this cocktail produces synergistic antinociception via both intra-locus coeruleus infusion and systemic administration, consistent with selective pharmacological dampening of pronociceptive tone from this neural circuit differentially. Furthermore, genetic deletion of mu opioid receptor across efferent-based modules in locus coeruleus demonstrated that intermodular interactions are essential for both mu opioid receptor-mediated physiological nociception and such pharmacological synergy. This framework has broad utility for selective targeting of other neural circuits under different physiological and pathological states, facilitating non-genetic translational applications arising from cell type-selective discoveries.

Disclosures: C. Kuo: None. J.G. McCall: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.07/H2

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS126451

Title: Connectopic maps of striatal dopaminergic projections in chronic low-back pain

Authors: *M. R. COLE¹, Z. ZHANG², P. Y. GEHA³;

¹Univ. of Rochester, Rochester, NY; ²UNC Chapel Hill, Chapel Hill, NC; ³Psychiatry, Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: In 2019, the National Center for Health Statistics reported that 39% of US adults experienced back pain, making it the most common site of pain. This condition is linked to a variety of both long- and short-term health effects, including diminished quality of life and increased healthcare costs. Additionally, the CDC estimated in 2018 that over 20% of US adults suffered from chronic pain, which is associated with its own list of co-morbidities, particularly substance misuse. Currently, there are no objective measures of chronic pain, no diagnostic or prognostic tools, and no cure. Therefore, understanding the mechanisms behind chronic pain - especially after any physical causes have healed - is essential. Recent evidence suggests that the development of chronic pain may be related to pre-existing variations in the structure and function of the nervous system. Specifically, chronic back pain appears to be associated with changes in dopamine transmission within the striatum. However, conducting large-scale studies using PET to image dopamine receptors is challenging due to the high cost and low resolution of PET imaging. Resting-state functional MRI (rs-fMRI) presents a more affordable alternative at higher resolutions, yet it typically cannot explore the pathophysiology of conditions through dopamine-opioid interactions. In this study, we utilized a cutting-edge technique called Connectopy, which allows us to associate the topological connectivity profile of rs-fMRI with dopaminergic projections within the striatum. Connectopy is a fully data-driven approach that produces continuous maps of the connection topography (connectopic maps) between regions of interest (the striatum and cortex for this study) through rs-fMRI which should be both generalizable and reproducible across different studies. After identifying a connectopic map that correlates to a map of dopaminergic projections derived from the DAT/SPECT images provided by the Parkinson's Progression Markers Initiative, we applied a general linear model to this map, testing for differences between chronic low-back pain (N=27) and healthy controls (N=27). Our analysis revealed a significant difference (p-value < 0.05) between the chronic pain and healthy controls in the right dorsal striatum, after correcting for multiple comparisons using threshold-free cluster enhancement (TFCE) with 5000 permutations. These results validate the application of Connectopy in studying - though indirectly - striatal dopaminergic transmission in chronic pain and corroborate that changes in dopaminergic transmission within the striatum are associated with chronic back pain.

Disclosures: M.R. Cole: None. Z. Zhang: None. P.Y. Geha: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.08/H3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 5R01NS112632-05
ASRA Pain Medicine Graduate Student Award

Title: Sphingosine-1-phosphate receptor signaling can regulate synaptic activity of corticotropin-releasing hormone expressing neurons in the central amygdala from chronic pain mice

Authors: *R. C. HINES^{1,2}, P. L. SHEETS^{1,2};

¹Pharmacol. and Toxicology, ²Stark Neurosciences Res. Inst., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: A key brain structure in the processing of chronic pain is the central nucleus of the amygdala (CeA), which has justifiably been termed the “nociceptive amygdala”. A major subclass of CeA neurons expressing corticotropin-releasing hormone (CRH; CeA^{CRH+} neurons) is sensitized in the acute, but not chronic, stage of neuropathic pain. There is a knowledge gap in the signal transduction regulation of synaptic activity in CeA^{CRH+} neurons. To address this gap in understanding, our lab has focused on the bioactive sphingolipid sphingosine-1-phosphate (S1P), which has differential reported effects on pain dependent on location within the central nervous system (CNS). S1P interacts with five G protein-coupled S1P receptor subtypes (S1PR₁₋₅), S1PR₁ being the most abundantly expressed in the brain. In this study, we dissected the modulation of CeA^{CRH+} neuron synaptic activity by S1PR₁ signaling in the spared nerve injury (SNI) mouse model of neuropathic pain (negative control: sham surgery). On post-operative day 14 (POD14; intermediate stage) we performed whole-cell patch clamp electrophysiological recordings on labeled CeA^{CRH+} neurons in acute brain slices, while pharmacologically manipulating the S1PR₁ signaling pathway. We found an S1PR₁ agonist, SEW2871, significantly reduces the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) recorded from CeA^{CRH+} neurons from sham mice. Interestingly, while SNI had no impact on sEPSCs onto CeA^{CRH+} neurons, the effect of SEW2871 seen in neurons from sham mice was lost in SNI mice. An S1PR₁ antagonist, NIBR-0213, had no effect on sEPSCs recorded from CeA^{CRH+} neurons from either sham or SNI mice, indicating there is possibly a mechanism during SNI which causes internalization of S1PR₁ on presynaptic excitatory inputs to CeA^{CRH+} neurons. We also show SNI increases the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from CeA^{CRH+} neurons. SEW2871 had no effect on sIPSCs onto CeA^{CRH+} neurons in sham mice, however, was able to significantly reduce sIPSCs onto CeA^{CRH+} neurons in SNI mice, similar to levels found in CeA^{CRH+} neurons from sham mice. This raises the possibility the expression of S1PR₁ on inhibitory inputs to CeA^{CRH+} neurons is increased by SNI. Our results indicate SNI affects excitatory and inhibitory inputs onto CeA^{CRH+}, and each type of input is differentially modulated by S1PR₁ signaling. We propose this differential modulation is due to differential S1PR₁ expression. These findings implicate CeA^{CRH+} in the processing of neuropathic pain and identify S1PR₁s as a potential target for the development of new analgesic pharmacotherapies.

Disclosures: R.C. Hines: None. P.L. Sheets: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.09/H4

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NS112632
American Society of Regional Anesthesia and Pain Medicine Graduate Student Award

Title: Sphingosine-1-phosphate receptor 1 agonism reduces inflammatory pain behavior via modulation of somatostatin-expressing neurons in the central amygdala

Authors: R. HINES¹, S. LAMERAND³, B. K. TAYLOR⁴, *P. L. SHEETS²;

¹Dept. of Pharmacol. and Toxicology, ²Indiana Univ. Sch. of Med., Indianapolis, IN; ⁴Dept. of Anesthesiol., ³Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The central nucleus of the amygdala (CeA) is a key brain structure in the processing of chronic pain and has justifiably been termed the “nociceptive amygdala.” A major subclass of CeA neurons expressing somatostatin (SST; CeA^{SST+} neurons) is inhibited in the acute stages of pain. There is a knowledge gap in the signal transduction regulation of synaptic and intrinsic activity in CeA^{SST+} neurons. To address this gap in understanding, our labs have focused on the bioactive sphingolipid sphingosine-1-phosphate (S1P) whose pathways have been established as a promising therapeutic target for treating multiple sclerosis with approved drugs currently being administered clinically. In this study, we dissected the modulation of CeA^{SST+} neuron synaptic activity by S1PR₁ signaling in the complete Freund’s adjuvant (CFA) mouse model of inflammatory pain (negative control: saline). We found chemogenetic inhibition of CeA^{SST+} neurons in uninjured male mice induced mechanical hypersensitivity, which was attenuated by intra-CeA administration of the S1P receptor 1 (S1PR₁) agonist, SEW2871 (1 µg/0.2 µL). In addition, injection of SEW2871 into the CeA attenuated mechanical hypersensitivity in the CFA model at post-operative day 3 (POD3; peak stage). We performed whole-cell patch clamp electrophysiological recordings on labeled CeA^{SST+} neurons in acute brain slices from CFA mice. Our preliminary data indicate that exogenous application of SEW2871 (100 nM) enhances the intrinsic excitability of CeA^{SST+} neurons recorded from POD3 CFA mice. Our preliminary data also show find that the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) onto CeA^{SST+} neurons is reduced in CFA-POD3 mice. However, SEW2871 did not have a significant effect on sEPSC frequency, but early indications are that it increases sEPSC amplitude measured in CeA^{SST+} neurons recorded from POD3 CFA mice. These findings implicate S1PR₁ as a potential target for the treatment of inflammatory pain via modulation of CeA^{SST+} neurons.

Disclosures: R. Hines: None. S. Lamerand: None. B.K. Taylor: None. P.L. Sheets: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.10/H5

Topic: E.01. Somatosensation – Pain and Itch

Support: NINDS T32 5T32NS115664

Title: Uncovering the Central Neural Mechanisms Underlying Sickness-Induced Hyperalgesia

Authors: *J. NGUYEN, J. OSTERHOUT;
Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: In response to infection, the brain generates stereotyped symptoms, including fever, fatigue, decreased appetite, hyperalgesia, and altered social interactions, ultimately promoting survival. Despite their critical role during an immune response, the neural basis for many sickness behaviors remains largely unknown. Hyperalgesia is a hallmark feature of infection. While much is known about how local inflammation can increase the excitability of nociceptive neurons, whether additional mechanisms are required for full-body hyperalgesia seen during systemic infection remains unclear. We recently uncovered a central humoral mechanism underlying the induction of select sickness symptoms through direct immune activation of neurons in the brain during systemic infection, suggesting that central immune sensitization may also play a key role in sickness-induced hyperalgesia. Using intraperitoneal injection of lipopolysaccharides (LPS) to model systemic infection, we identified a population of neurons in the ventral bed nucleus stria terminalis (vBNST) that are activated by LPS and noxious stimuli, suggesting a node at the intersection of pain and sickness. To test whether LPS-sensitive vBNST (vBNST^{LPS}) neurons that are activated during systemic infection are sufficient to generate pain responses, we utilized cre-dependent, viral-mediated functional manipulation to activate vBNST^{LPS} neurons. We found a significant impact on mechanical and thermal pain responses upon activation, indicating that vBNST^{LPS} neurons are sufficient to induce hyperalgesia. Furthermore, we observed sexually dimorphic responses with mechanical but not thermal pain. To test whether vBNST^{LPS} neurons are necessary for driving increased pain sensitivity, we ablated vBNST^{LPS} neurons and found reduced mechanical pain sensitivity during systemic inflammation, indicating that vBNST^{LPS} neurons are necessary to induce mechanical hyperalgesia. Single-nucleus RNA sequencing identified key markers for vBNST^{LPS} neurons and specific expression of immune receptors. Our results suggest that LPS-responsive neurons in the brain can mediate pain sensitivity and that central immune sensitization may play a key role in hyperalgesia and allodynia during sickness. Funding: R00NS114107, 5T32NS115664.

Disclosures: J. Nguyen: None. J. Osterhout: None.

Poster

PSTR021: Subcortical Pain Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR021.11/H6

Topic: E.01. Somatosensation – Pain and Itch

Title: Exploration of ECT-related memory loss through local field potentials in anesthetized rats

Authors: *D. IBARRA¹, J. TREJO², Y. B. PENG³;

²Psychology, ³Dept Psychol, Life Sci. Bldg., ¹Univ. of Texas at Arlington, Arlington, TX

Abstract: Since its first application in 1938, Electroconvulsive therapy (ECT) has been used as a last-line intervention to improve severe symptoms of several mental health conditions (e.g., major depression, schizophrenia, mania etc.) when previous treatments have failed. Although ECT can be an effective tool, there are some adverse effects associated with its use, such as experiencing temporary memory impairments after ECT. Considering that chronic pain affects millions and often leads to drug dependence, ECT has also been applied to treat certain chronic pain conditions. This study aims to explore whether ECT can disrupt pain-related memories as a potential non-pharmacological strategy for long-term pain relief. It is hypothesized that ECT will disrupt pain memory as a partial mechanism of pain relief. Local field potentials (LFPs) in combination with ECT were used to test the neural dynamics across five frequency bands (delta 0.3 - 3 Hz, theta 3 - 7 Hz, alpha 7 - 12 Hz, beta 12 - 30 Hz, and gamma 30 - 100 Hz) in four distinct regions in the rat brain: anterior cingulate cortex (ACC), right central amygdala (R-CeA), hippocampal subregions CA1 and CA3. Under isoflurane anesthesia, the LFP was recorded in two separate conditions: formalin-only (pain) and ECT post-formalin. The formalin (50µl at 3%) was injected into the left hind paw. The ECT was delivered at parameters consisting of a combination of 50 pulse/s, 0.7 ms, 2 s at 50 mA, 3 times 12-15 s apart. Results reveal that the formalin injection increases power across all five frequency bands. The application of ECT after formalin injection displays a mixed inhibition or facilitation in the five frequency bands. These observed ECT effects on LFP responses require further study in awake animals to correlate behavioral change with LFP changes.

Disclosures: D. Ibarra: None. J. Trejo: None. Y.B. Peng: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.01/H7

Topic: E.01. Somatosensation – Pain and Itch

Support: VR Project Grant 2021-03054
VR Project Grant 2022-00564

Stockholm County Council (ALF) RS 2023-0859
Donation Leif Lundblad and family
Reumatikerförbundet R-993000

Title: Electrophysiological Evidence for the Involvement of Muscle Spindle Afferents in Somatic Allodynia in Fibromyalgia Patients

Authors: *S. H. LINDSTROM¹, A. G. MARSHALL^{2,3,1}, A. MARSHALL^{2,1}, A. U. BJERKHAUG^{4,5}, J. S. DUNN⁶, E. KOSEK^{4,5}, D. A. MAHNS⁶, H. OLAUSSON¹, S. S. NAGI^{1,6};
¹Dept. of Biomed. & Clin. Sci., Linköping Univ., Linköping, Sweden; ²Univ. of Liverpool, Liverpool, United Kingdom; ³The Walton Ctr., Liverpool, United Kingdom; ⁴Karolinska Inst., Stockholm, Sweden; ⁵Uppsala Univ., Uppsala, Sweden; ⁶Sch. of Med., Western Sydney Univ., Sydney, Australia

Abstract: Introduction: Fibromyalgia is a chronic pain condition affecting 2%-8% of the world population. While abnormal skin innervation and sensitization of cutaneous nociceptors have been described, it is unclear how these changes relate to Fibromyalgia pain as Fibromyalgia patients typically report widespread deep muscle pain. Further, Fibromyalgia patients often suffer from balance and proprioception deficits. Muscle spindle afferents (MSAs) play an essential role in proprioception and are easily targeted for study with microneurography. Unfortunately, the contribution of MSAs to Fibromyalgia pain is relatively unexplored. Therefore, we aimed to examine whether MSAs can play a role in the deep muscle pain typically reported by Fibromyalgia patients. **Methods:** Participants with Fibromyalgia and healthy controls (HC) underwent microneurography of the proximal radial nerve using a high-impedance electrode. After establishing stable recordings from individual MSAs, we delivered intraneural microstimulation (INMS) via the same electrode to selectively activate the recorded MSA. Current pulses were delivered at 1-Hz or 20-Hz, with the amplitude increased in 1- μ A increments until either percept or motor threshold was reached. During test stimulations, current strength was set to percept threshold (or 80% of motor threshold, if no percept). During 3 repeats of the stimulus train (20-Hz for 30-sec) the participant continuously reported pain intensity using an electronic visual analogue scale. Standardized questionnaires assessed the quality of evoked sensations after test stimulation was completed. **Results:** The current amplitudes used during test stimulations were comparable between HC and Fibromyalgia. INMS of MSAs was never painful in HC, although some participants noted non-painful sensations. In contrast, Fibromyalgia patients reported deep pain with rapid onset during INMS of MSAs. This pain was localized to the muscle innervated by the stimulated MSA, and was described as aching, cramping, burning, tiring/exhausting, and "similar to Fibromyalgia pain". **Conclusion:** These findings suggest that MSAs contribute to the deep somatic allodynia observed in Fibromyalgia patients.

Disclosures: S.H. Lindstrom: None. A.G. Marshall: None. A. Marshall: None. A.U. Bjerkhaug: None. J.S. Dunn: None. E. Kosek: None. D.A. Mahns: None. H. Olausson: None. S.S. Nagi: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.02/H8

Topic: E.01. Somatosensation – Pain and Itch

Support: Swedish Research Council Starting Grant no. 2020-01107
Knut and Alice Wallenberg Foundation Fellowship
Swedish Research Council Project Grant no. 2021-03054
Knut and Alice Wallenberg Project Grant no. 2019.0047
Knut and Alice Wallenberg Clinical Scholar Grant no. 2019.0487
ALF Grants Region Östergötland
Swedish Society of Medicine Project Grant

Title: Piezo2-dependent rapid pain system in humans

Authors: ***M. BRODZKI**¹, O. BOUCHATTA¹, H. MANOUZE¹, G. BASILE CARBALLO¹, H. YU², E. KINDSTRÖM¹, F. MEIRA DE FARIA¹, O. THORELL^{1,3}, A. KAO⁴, J. LILJENCRA NTZ^{5,6}, C. KARLSSON¹, M. MAIDANA CAPITAN¹, K. K. NG¹, E. FRANGOS⁵, B. RAGNEMALM¹, D. SAADE⁷, I. SZCZOT¹, W. MOORE⁸, K. TEREJKO^{1,9}, G. J. GERLING¹⁰, D. A. MAHNS³, M. LARSSON¹, W. LUO², A. MARSHALL^{1,8}, A. T. CHESLER^{5,7}, H. OLAUSSON¹, S. S. NAGI^{1,3}, M. SZCZOT¹;

¹Ctr. for Social and Affective Neurosci., Linköping Univ., Linköping, Sweden; ²Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA; ³Sch. of Med., Western Sydney Univ., Sydney, Australia; ⁴Sch. of Engin. and Applied Sci., Univ. of Virginia, Charlottesville, VA; ⁵Natl. Ctr. for Complementary and Integrative Hlth., Bethesda, MD; ⁶Dept. of Anesthesiol. and Intensive Care, Sahlgrenska Acad. at Univ. of Gothenburg, Gothenburg, Sweden; ⁷Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; ⁸Inst. of Life Course and Med. Sci., Univ. of Liverpool, Liverpool, United Kingdom; ⁹Biol. of Astrocytes Res. Group, Łukasiewicz Res. Network - PORT Polish Ctr. for Technol. Develop., Wrocław, Poland; ¹⁰Systems and Information Engineering, and Biomed. Engin., Univ. Of Virginia, Charlottesville, VA

Abstract: The diversity of mechanical pain sensations in humans cannot be explained based on our current understanding of pain-sensing neural classes in the skin. To begin to bridge this gap, we dissected the neural basis of a distinct form of pain sensation evoked by hair pulling in humans. Based on observations in a rare group of individuals with PIEZO2 deficiency syndrome, we demonstrated that hair-pull pain is dependent on PIEZO2 transduction. Single-unit axonal recordings revealed a specific class of cooling-responsive, rapidly conducting nociceptors that are selectively tuned to painful hair-pull stimuli. We pharmacologically mapped these nociceptors to a specific transcriptomic class and demonstrated that myelinated nociceptors are anatomically associated with hair follicles. Using functional imaging in mice, we demonstrated that in a homologous nociceptor, Piezo2 is necessary for high-sensitivity, robust activation by hair-pull stimuli. Finally, studies in control participants showed that noxious hair-pull stimuli trigger a distinct nociceptive response, including a rapid nociceptive reflex; further, observations in rare A β -deafferented individuals and nerve conduction block studies revealed that hair-pull pain perception is dependent on A β -fiber input. Together, we identified a previously unknown class of human nociceptors and characterized its functional and molecular features.

Disclosures: M. Brodzki: None. O. Bouchatta: None. H. Manouze: None. G. Basile Carballo: None. H. Yu: None. E. Kindström: None. F. Meira de Faria: None. O. Thorell: None. A. Kao: None. J. Liljencrantz: None. C. Karlsson: None. M. Maidana Capitan: None. K.K. Ng: None. E. Frangos: None. B. Ragnemalm: None. D. saade: None. I. Szczot: None. W. Moore: None. K. Terejko: None. G.J. Gerling: None. D.A. Mahns: None. M. Larsson: None. W. Luo: None. A. marshall: None. A.T. Chesler: None. H. Olausson: None. S.S. Nagi: None. M. Szczot: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.03/H9

Topic: E.01. Somatosensation – Pain and Itch

Support: Versus Arthritis 22471
Pain Relief Foundation

Title: Influence of small fibre neuropathy on C-nociceptor hyperexcitability in fibromyalgia

Authors: *A. MARSHALL¹, W. MOORE¹, J. BURGESS¹, A. MAKDANI², J. P. DUNHAM³, U. ALAM¹, A. MARSHALL¹;

¹Univ. of Liverpool, Liverpool, United Kingdom; ²Liverpool John Moores Univ., Liverpool, United Kingdom; ³Univ. of Bristol, Bristol, United Kingdom

Abstract: Introduction: Fibromyalgia (FM), the most common form of chronic widespread pain, affects 2%-8% of the world population. The pathophysiology of FM remains unknown but abnormal peripheral innervation and sensitisation, and abnormal axonal properties of cutaneous nociceptors have been described. However, the relationship between abnormal peripheral innervation and nociceptor sensitisation is not clear. Therefore, using a within subjects' design, we aimed to determine whether evidence of sensitisation and altered axonal properties of nociceptors, tested during microneurography, segregated with altered skin innervation. **Methods:** Participants with FM (N=20) and healthy controls underwent assessment of demographic and anthropometric measures; clinical and pain phenotyping using standardised questionnaires; skin biopsy to assess intraepidermal nerve fibre density; and multiple-single afferent recording of nociceptors in the superficial peroneal nerve using microneurography. Participants with FM were segregated into the presence or absence of small fibre pathology using normative data from our healthy control cohort. C-fibre nociceptors were classified as type 1A and type 1B according to their characteristic profile of activity-dependent slowing of conduction velocity (CV). Neural parameters included CV, percentage CV slowing during electrical stimulation paradigms, and the presence or absence of spontaneous activity or mechanical sensitisation. **Results:** Approximately half of the participants with FM had evidence of abnormal skin innervation at the distal leg. Mechanical sensitisation (11/26 fibres; 6/11 participants) and spontaneous activity (5/26 fibres; 4/11 participants) of type 1B nociceptors was only seen in the group with FM. There was a trend

for type 1B nociceptors from FM participants with abnormal skin innervation to have a lower CV and have a greater proportion of fibres exhibiting mechanical sensitisation and/or spontaneous activity. Individuals with FM with mechanically sensitised type 1B nociceptors also had a trend for higher total PainDetect but not overall FIQR scores. **Conclusion:** The findings confirm a high incidence of abnormal innervation of the epidermis and the presence of hyperexcitability of type 1B 'silent' nociceptors in individuals with chronic pain due to FM. Hyperexcitability in type 1b nociceptors may contribute to a more severe neuropathic like pain phenotype.

Disclosures: A. Marshall: None. W. Moore: None. J. Burgess: None. A. Makdani: None. J.P. Dunham: None. U. Alam: None. A. Marshall: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.04/H10

Topic: E.01. Somatosensation – Pain and Itch

Title: The p65 subunit of NF-kB is required for the establishment of REM sleep deprivation-induced mechanical allodynia in female rats

Authors: *C. J. MARTÍNEZ MAGAÑA¹, J. MURBARTIÁN²;

¹Pharmacobiology, Cinvestav, Sede Sur, Ciudad de México, Mexico; ²Pharmacobiology, Cinvestav, Sede Sur, Ciudad de Mexico, Mexico

Abstract: Sleep disturbances (insomnia, reduced sleep time) are frequently associated with the development of nociplastic pain (dysfunctional pain) in humans. Specifically, REM sleep deprivation (REM-SD) causes a decrease in the thresholds to detect thermal and mechanical stimuli in humans and rodents. So far, the mechanisms involved in this phenomenon are not clearly understood. Previously, our research group reported that REM-SD for 48 h leads to the development of mechanical allodynia in rats of both sexes. The pretreatment with minocycline or BMS-345541, two drugs that have an inhibitory effect on the transcription factor NF-kB, prevents the establishment of mechanical allodynia in female, but not in male rats, exposed to REM-SD. In this study, we investigated whether REM-SD modifies the expression of two NF-kB family proteins (p50 and p65) in the dorsal root ganglia (L4 & L5) and in the spinal cord (lumbar section) of rats. In addition, we evaluated the binding to DNA of the p65 NF-kB in nuclear extracts from the spinal cord. Finally, we assessed the impact of depletion of NF-kB on the development of REM sleep deprivation-induced allodynia. The results show that female rats exposed to REM-SD exhibited a notable increase in the expression of p50, p65, and phosphorylated p65 (P-p65) proteins in the dorsal root ganglia and spinal cord. In contrast, male rats exposed to REM sleep deprivation showed a modest increase in p65 protein only in the spinal cord. Moreover, REM-SD increased p65 binding to DNA in the spinal cord in female rats but not males. Finally, we found that in NF-kB/p65-depleted female rats, REM-SD did not

induce mechanical allodynia. Meanwhile, the effect of p65 depletion in males was smaller than that observed in females. In conclusion, our study results suggest that p65 NF- κ B is involved in developing REM sleep deprivation-induced mechanical allodynia, mainly in females, and it has a lesser role in male rats. Further studies of the influence of biological sex on the mechanisms involved in the development of this and other types of pain are needed.

Disclosures: C.J. Martínez Magaña: None. J. Murbartián: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.05/H11

Topic: E.01. Somatosensation – Pain and Itch

Title: Transcriptomic Profiling of Human iPSC-derived Sensory Neurons as a Model for Non-Opioid Pain Therapeutic Drug Discovery

Authors: S. SCHACHTELE, L. ZEIGHAMI, Y. RAJ, R. FIENE, L. HARMS, K. BAKSHY, *A. FATHI, C. B. CARLSON;
FUJIFILM Cell. Dynamics, Madison, WI

Abstract: With the recent FDA approval of several NaV1.8 sodium channel inhibitors, there is a renewed research focus on non-opioid based targets for pain. Concomitantly, the desire to improve preclinical model predictability over historical rodent models is fueling interest in new human-relevant models, with an emphasis on induced pluripotent stem cell (iPSC)-derived peripheral sensory neurons. In this study, we report the large-scale, directed differentiation of human iPSC-derived sensory neurons (a.k.a., iCell Sensory Neurons from FUJIFILM Cellular Dynamics) and established a baseline transcriptomic characterization of these cells in comparison to human dorsal root ganglion (hDRG) and published iPSC-derived sensory neuron protocols. Briefly, iCell Sensory Neurons were cultured in complete medium for 21 days post thaw and RNA was extracted for either bulk or single-cell (sc) RNA sequencing (RNASeq). Published RNASeq datasets for both iPSC-derived sensory neurons and hDRG were downloaded from Gene Expression Omnibus (GEO). Cell-based assays were also performed on sensory neurons to evaluate functional responses to sensory agonists and validate other sensorineural functions. Using a common set of sensory neuron markers, we found that iPSC-sensory neuron protocols cluster distinctly from hDRG. Within the iPSC-sensory neurons, subclusters were identified indicating variation of differentiation protocol impacts the final sensory neuron populations. By comparison, iCell Sensory Neurons showed high expression of non-opioid pain-relevant genes (i.e., SCN9A, SCN10A, TRPV1, PEIZO2, and P2RX3), which was corroborated by scRNA-seq. In addition, these neurons highly express neural maturation transcription factors with concomitant low expression of progenitor markers, supporting a state of terminal differentiation and advanced maturation. The prominent expression of calcium handling genes, sodium channels, and potassium channels correlate with robust calcium influx in response to

sensory agonists (i.e., capsaicin). In addition, the genetic profile of iCell Sensory Neurons shows alignment with trigeminal ganglion markers, which aligns with the ability of the cells to secrete CGRP and show SNAP25 cleavage in response to Botulinum toxin. In summary, iPSC-derived sensory neurons have a transcriptome profile relevant for human *in vitro* modeling of pain and neuropathy. Importantly, iCell Sensory Neurons express premier non-opioid pain targets within a population that is enriched in ion channels and intracellular signaling pathways that correlate with advanced sensory function.

Disclosures: **S. Schachtele:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc. **L. Zeighami:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc. **Y. Raj:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc. **R. Fiene:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc. **L. Harms:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc. **K. Bakshy:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc. **A. Fathi:** A. Employment/Salary (full or part-time): Fujifilm Cellular Dynamics Inc. **C.B. Carlson:** A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics Inc..

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.06/H12

Topic: E.01. Somatosensation – Pain and Itch

Title: Chemotherapy-induced mitochondrial dysfunction and neuronal damage in iPSC-derived sensory neurons

Authors: ***I. SCHILCHER**, S. KRASSNIG, T. LÖFFLER, I. PEREZ-RUIZ, M. DAURER, A. ZDOUC, S. FLUNKERT, M. PROKESCH;
Scantox Neuro GmbH, Grambach, Austria

Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) remains a major clinical challenge, often limiting effective cancer treatment. CIPN affects a significant proportion of cancer patients, manifesting as chronic pain, numbness, and sensory deficits. Traditional research models, such as rodents, often fail to recapitulate human-specific neuronal responses to chemotherapeutics. iPSC-derived sensory neurons offer a scalable, patient-relevant system to study neurotoxicity *in vitro*. Paclitaxel and oxaliplatin, two commonly used chemotherapeutic agents, are known to disrupt mitochondrial function and induce apoptosis in sensory neurons, which underlies CIPN. Modelling these effects in iPSC-derived sensory neurons enables mechanistic insights and supports the development of targeted interventions to alleviate CIPN. We employed human-induced pluripotent stem cell (iPSC)-derived sensory neurons to model CIPN and evaluate neurotoxicity induced by paclitaxel and oxaliplatin. Using CellTiter-Glo and TMRM assays, we observed a dose-dependent reduction in neuronal viability and mitochondrial membrane potential, indicating mitochondrial dysfunction and cytotoxicity. Additionally, more

subtle alterations in neuronal morphology, neurite fragmentation, outgrowth, and activity were analyzed using confocal microscopy and live-cell imaging. The current study validates iPSC-derived sensory neurons as a translationally relevant platform for mechanistic studies and preclinical screening of neuroprotective strategies against CIPN.

Disclosures: **I. Schilcher:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **S. Krassnig:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **T. Löffler:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **I. Perez-Ruiz:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Daurer:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **A. Zdouc:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **S. Flunkert:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.07/H13

Topic: E.01. Somatosensation – Pain and Itch

Title: Redefining pain assessment: combining wearables technologies and AI for continuous and multidimensional monitoring

Authors: ***A. CIMOLATO**¹, A. SPARAPANI¹, N. GOZZI², G. AURUCCI², J. METZGER³, A. BELLITTO⁴, A. MASSONE⁵, M. HUBL³, A. CURT³, B. LEGER⁶, S. RASPOPOVIC¹;
¹Ctr. for Med. Physics and Biomed. Engin., Med. Univ. of Vienna, Vienna, Austria; ²D-HEST, ETH Zurich, Zurich, Switzerland; ³Spinal Cord Injury Center, Balgrist Univ. Hosp., Univ. of Zurich, Zurich, Switzerland; ⁴Cognitive Robotics Department, Fac. of Mechanical Engin., Delft Univ. of Technol., Delft, Netherlands; ⁵Spinal Cord Italian Lab, Unità Spinale Unipolare, Santa Corona Hosp., Pietra Ligure, Italy; ⁶Inst. for Res. in Rehabil., Clinique Romande de Réadaptation SuvaCare, Sion, Switzerland

Abstract: Chronic pain is a complex, multidimensional condition that remains difficult to assess and manage, largely due to continued reliance on retrospective self-reports and limited clinical endpoints. These traditional tools often fail to capture the dynamic physiological and psychosocial aspects of the pain experience. To address this gap, we developed a digital health platform enabling continuous, remote, and multidimensional assessment of pain in patients' natural environments.

We evaluated this system in a multi-center observational study involving individuals with chronic pain from diverse etiologies. Over a 14-day period, participants continuously wore a smartwatch device that recorded physiological signals including heart rate, blood volume pulse, and skin conductance. In parallel, they completed app-based ecological momentary assessments of pain and standardized psychological surveys. The platform achieved high compliance,

confirming its feasibility for real-world, at-home use.

Our findings challenge the conventional practice of infrequent, single-question pain assessments, revealing that pain is indeed a multidimensional and rapidly fluctuating experience that cannot be accurately captured by isolated, retrospective reports. Moreover, multimodal data analysis revealed strong associations between daily pain reports and psychosocial states. At the same time, physiological patterns showed significant correlations with self-reported pain levels. These results support the potential for objective, noninvasive pain detection.

This work highlights the importance of integrating subjective and objective data for comprehensive pain profiling and underscores the potential of digital tools to support personalized treatment decisions in clinical practice.

Disclosures: A. Cimolato: None. A. Sparapani: None. N. Gozzi: None. G. Aurucci: None. J. Metzger: None. A. Bellitto: None. A. Massone: None. M. Hubli: None. A. Curt: None. B. Leger: None. S. Raspovic: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.08/H14

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01 NS132483
NIH R01 NS131560
NIH R01 AR081887-01S1
NIH 2T32AR064194-11

Title: Human embryonic cell line displays properties of nociceptive sensory neurons: a new pipeline for screening pain therapies

Authors: *S. A. DOCHNAL¹, Y. DU⁴, K. FRANCO MALANGE⁵, J. B. LEMES², D. BANDARI³, K. B. DORE⁷, Y. MILLER⁸, T. L. YAKSH⁶;

¹Anesthesiol. & Pharmacol., ²Anesthesiol., UCSD, San Diego, CA; ³UCSD, La Jolla, CA; ⁴Dept. of Neurosciences, Univ. of California San Diego, La Jolla, CA; ⁵Anesthesiol. & Pharmacol., Univ. California San Diego, San Diego, CA; ⁶Univ. California San Diego, La Jolla, CA; ⁷Neurosciences, UCSD Dept. of Neurosciences, La Jolla, CA; ⁸UC San Diego, La Jolla, CA

Abstract: Nociceptors within the dorsal root ganglion (DRG) detect and relay painful stimuli from the periphery to the brain, and disruption of this process leads to sustained pain states. The study of nociceptors in animal models has been crucial in our understanding of pain sensation. However, there are essential molecular, cellular, and electrophysiological differences between human and animal model DRG neurons. Therefore, a complementary *in vitro* model of human nociceptors is likely required for successful pain therapy development. We systematically characterized the nociceptive properties of differentiated human DRG-derived immortalized

HD10.6 cells. Using immunofluorescence, we reported the abundance and localization of nociceptive machinery central to regulating excitability and linked with pain sensation in DRG neurons including ion channels, excitatory receptors, and afferent peptides (N=3). Using calcium imaging, we illustrated the electrical functionality of these channels (N=3). Using whole cell patch clamping, we reported similar baseline electrophysiological parameters of HD10.6 cells to those previously observed in human patient donor DRGs (N=2). Further, human nociceptors are notoriously sensitive to opioids which inhibit the transmission of pain signals. We show that HD10.6 cells abundantly express mu opioid receptor 1 and a specific mu opioid agonist reverses heightened calcium influx within mature HD10.6 cells (N=3), mirroring the physiological response to opioids in humans. Importantly, we optimized the culture of HD10.6 cells into microfluidic devices (N=3), in which we can separately stimulate and/or survey the soma and terminal axon of the nociceptor. This isolation is important as it mirrors human anatomy, and the soma and axons are in contact with differential local/circulating inflammatory products and non-neuronal cells in a given pain state. We also demonstrated the ability of the HD10.6 cells to undergo increased calcium influx events indicative of sensitization in response to IL-6 agonist Oncostatin M (N=3). Therefore, we have created a new model to study not only human nociceptor physiology, but “human pain in a culture dish”. Using several distinct approaches, we have validated a new, physiologically relevant, and reproducible system of human-derived nociceptors. This system is now being employed to investigate mechanisms of, and screen species-specific therapies for, a variety of pain states, including post-herpetic neuralgia, cancer pain, and rheumatoid arthritis.

Disclosures: S.A. Dochnal: None. Y. Du: None. K. Franco Malange: None. J.B. Lemes: None. D. Bandari: None. K.B. Dore: None. Y. Miller: None. T.L. Yaksh: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.09/H15

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant MH076136
NIH grant R01EB026549

Title: Social information creates self-fulfilling prophecies in judgements of pain, vicarious pain, and cognitive effort

Authors: *A. YAZDANPANA¹, H. JUNG², A. SOLTANI¹, T. D. WAGER¹;

¹Psychological and Brain Sci., Dartmouth Col., Hanover, NH; ²Stanford Univ., Stanford, CA

Abstract: Social learning can shape expectations and perception and, when strong enough, lead to self-fulfilling prophecies such as placebo effects that persist or grow over time. While well-documented across contexts, it remains unclear whether *unreinforced* social cues—never

confirmed by actual outcomes—can produce lasting perceptual changes despite repeated disconfirming feedback. To test this, 111 participants completed three tasks: (1) somatic pain (thermal stimulation), (2) vicarious pain (videos of others in pain), and (3) cognitive effort (mental rotation). Each task included stimuli at three pre-normed intensity levels. Critically, each trial was preceded by a social cue—ostensibly the average rating of 10 peers—randomly set to indicate high or low intensity, independent of actual stimulus level. Participants rated perceived pain, observed pain, or effort at the end of each trial. Perceptual ratings were strongly biased in the direction of the social cue across all tasks, showing perceptual assimilation to expectations. Mediation analysis showed bidirectional effects between perceptual ratings and expectations. Reinforcement learning models revealed two mechanisms: (1) expectation-driven perceptual shifts and (2) confirmation-biased learning, where prediction errors (PE) inconsistent with the cue direction were downweighted. The neural correlates of the PE signals were found in multiple areas in the pain domain including somatosensory cortex and dorsal posterior insula. In the vicarious pain domain, this activity was found in the angular gyrus and inferior frontal gyrus—previously implicated in mentalizing and affective mirroring—with partial overlap with the pain network. In the cognitive effort task, prediction error signals were localized primarily to occipital regions, consistent with visual demands of the mental rotation. Together, these results demonstrate that social information, even when unreinforced, can generate self-fulfilling perceptual biases through shared computational mechanisms across domains but distinct neural correlates. Future model-based fMRI analyses will examine which brain regions track key variables—expectations, perception, and prediction errors—and test which learning models best explain the observed activity.

Disclosures: A. Yazdanpanah: None. H. Jung: None. A. Soltani: None. T.D. Wager: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.10/H16

Topic: E.01. Somatosensation – Pain and Itch

Title: Robust sensory neuron phenotype identified in human iPSC-derived sensory neurons using electrophysiological recordings

Authors: *S. SCHACHTELE¹, N. SECOMANDI², M. BERGAMINI², F. OLIVERO², E. B. STEVENS², A. FATHI¹, R. FIENE¹, C. B. CARLSON¹, A. M. RUSH²;

¹FUJIFILM Cell. Dynamics, Madison, WI; ²Metrion Biosci., Cambridge, United Kingdom

Abstract: Humanized models of pain are critical for confidently translating the effectiveness of therapeutic compounds from rodents to man. Human induced pluripotent stem cell (iPSC)-derived sensory neurons are emerging as a key in vitro human model of nociception that can bridge preclinical discovery data from cultured rodent dorsal root ganglion neurons or *in vivo* rodent models of pain to a human-relevant system. Despite initial success in generation of iPSC-

derived sensory neurons within academia/pharma, lengthy differentiation protocols, batch-to-batch variability or lack of clear sensory neuron phenotype has limited use of the model to support pain drug discovery. In this study, we evaluated the phenotype and robustness of a commercial source of human iPSC-derived sensory neurons (iCell Sensory Neurons) using gene expression and electrophysiology. These neurons, differentiated from a female donor (21527), exhibit high sensorineural purity (>80% BRN3A+/UCHL1+). Bulk RNASeq analysis in sensory neurons cultured for 21 days *in vitro* shows the expression of sensory neuron ion channels, including sodium channels (SCN9A, SCN10A) and sensory receptors (TRPV1, P2RX3, PIEZO2). Specifically, robust expression of Nav1.7 (SCN9A) was observed in the population. This was confirmed using single cell RNAseq analysis (21 days *in vitro*) where approximately 60% of neurons population expressed SCN9A. Electrophysiological properties of sensory neurons were recorded between 28 and 56 days *in vitro* using whole-cell patch clamp technique. In terms of passive membrane properties, there was a gradual hyperpolarization in resting membrane potential and increase in rheobase during time in culture. Evoked action potentials from the iPSC-derived sensory neurons displayed a waveform typical of human/rat DRGs, with a broad action potential and ‘hump’ in the repolarizing phase. Current injections evoked multiple firing, where the proportion of cells displaying multiple firing increased between 28 and 56 days in culture. Repetitive firing evoked by a current injection ramp protocol was inhibited by the selective Nav1.7 inhibitor, PF05089771 (100 nM), confirming the functional expression of Nav1.7. The presence of sensory neuron markers, excitability properties consistent with sensory neurons and evidence of nociceptor ion channels (using both RNASeq and electrophysiology) provides strong evidence that iCell Sensory Neurons have a robust sensory neuron phenotype suitable for supporting pain discovery programs.

Disclosures: S. Schachtele: None. N. Secomandi: None. M. Bergamini: None. F. Olivero: None. E.B. Stevens: None. A. Fathi: None. R. Fiene: None. C.B. Carlson: None. A.M. Rush: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.11/I1

Topic: E.01. Somatosensation – Pain and Itch

Title: Evaluating Capsaicin Responses and CGRP Release in Human Induced Pluripotent Stem Cell Derived Nociceptors

Authors: *V. TRUONG, D. ARORA, P. WALSH;
Anatomic Inc., Minneapolis, MN

Abstract: Nociceptors are specialized sensory neurons essential for detecting harmful stimuli and initiating protective pain responses. Two hallmark features of functional nociceptors are their sensitivity to capsaicin, a TRPV1 agonist that evokes a burning sensation, and their ability

to release calcitonin gene-related peptide (CGRP), a neuropeptide involved in neurogenic inflammation and migraine. Together, capsaicin-evoked activity and CGRP release serve as key functional readouts for in vitro validation, with applications in high-throughput screening of non-opioid analgesics, studies of inflammatory and neuropathic pain, ion channel modulation, and CGRP-targeted drug development. These human-relevant, animal-free models are also increasingly valuable in the cosmetics industry for evaluating the neuroinflammatory potential of topical compounds. Despite extensive efforts from the field, generating nociceptors from human pluripotent stem cells that consistently exhibit robust capsaicin sensitivity and CGRP release has proven difficult. Existing protocols either fail to develop capsaicin sensitivity at all, do not release CGRP upon stimulation or require protracted time in culture. In this study, we present a refined directed differentiation protocol and defined culture system and evaluated their responses to physiological concentrations of capsaicin (<1 uM) and their secretion levels of CGRP using multi-electrode array recordings and immunoassays. The goal of our research is to generate a fast, reproducible, and scalable approach for generating human nociceptors suitable for screening pain therapeutics, modeling disease mechanisms, assessing consumer product safety, and reducing reliance on animal models.

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

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.12/I2

Topic: E.01. Somatosensation – Pain and Itch

Title: Biophysical characterization of the Nav1.9 Na⁺ channel in human sensory neurons

Authors: ***P. SHI**¹, T. COTTA², I. J. OROZCO¹, G. PAGE³, N. ABI GERGES³, R. KONDO⁴, A. GHETTI¹, K. CARLIN⁵;

¹AnaBios, San Diego, CA; ²Neurophysiol., ³Anabios Corp., San Diego, CA; ⁴AnaBios Corp., San Diego, CA; ⁵Clin. Res., San Diego, CA

Abstract: Voltage-gated sodium channels (Nav) are crucial in generating rapidly propagating electrical signals in the human body. In human dorsal root ganglia (DRG), and trigeminal (TG) neurons, the tetrodotoxin (TTX)-sensitive Nav1.7, and TTX-resistant Nav1.8 play critical roles in the firing of action potentials, which drive electrical impulses to facilitate many downstream processes such as sensory perception, chronic itch, and pain. In particular, the inhibition of

Nav1.7 and/or Nav1.8 through pharmacology and knock-out mouse models has been shown to reduce pain sensitivity and both channels have been drug targets for analgesia for years. Recently, a renewed interest in the pharmaceutical field brings attention to a third sodium channel, Nav1.9, that is preferentially expressed in peripheral neurons and are abundantly present in both DRG and TG neurons. Nav1.9 is a TTX-resistant sodium channel, similar to Nav1.8, although, shows distinct biophysical properties. The channel exhibits both slower activation and slower inactivation kinetics that produces a persistent background current, which is thought to modulate resting membrane potential and cellular excitability. Genetic and functional studies found two gain-of-function mutations (R225C, and A808G) in Nav1.9 that leads to familial episodic pain syndrome, suggesting that Nav1.9 may be a promising pain target. However, the Nav1.9 channel's unique gating characteristics, pharmacology, and role in pain signaling, is still largely unclear. This is in part due to the lack of subtype-selective tool compounds, and relevant human data. Many of the previous biophysical characterizations were done in rodent models, and heterologous expression systems, which may lack many of the human native regulatory components. Here, we pharmacologically isolated and recorded the Nav1.9 currents, using both TTX and Suzetrigine (a potent, and selective Nav1.8 blocker), in human primary sensory neurons, and analyzed the biophysical properties of this channel. This information provides further insights into the Nav1.9 channel function which may aid future pharmacology and drug discovery efforts.

Disclosures: P. Shi: None. T. Cotta: None. I.J. Orozco: None. G. Page: None. N. Abi Gerges: None. R. Kondo: None. A. Ghatti: None. K. Carlin: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.13/I3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 1R43TR004743-01

Title: Development of a High-Throughput Human iPSC-Based Pain Assay Platform: Functional Characterization of Nociceptors for Analgesic Screening

Authors: *S. K. GILMORE-HALL¹, C. G. RINES³, L. HARRISON², A. SMITH², K. L. GORDON⁵, V. TRUONG⁶, P. WALSH⁷, B. TEKWANI⁸, J. PRICE⁴, P. MCDONOUGH⁹;
¹NeuroBiology, ²Vala Sci., San Diego, CA; ³Biol., ⁴Vala Sciences, Inc., San Diego, CA; ⁵Biol., Vala Sci. Inc., San Diego, CA; ⁶Stem Cell Engin., ⁷Anatomic Inc., Minneapolis, MN; ⁸Vala Sci. IN, San Diego, CA; ⁹Vala Sci. Inc, San Diego, CA

Abstract: Pain is a persistent human challenge, causing extensive human discomfort and loss of productivity. Current treatments for pain rely heavily on highly addictive opioids. With few effective, non-opioid, analgesics in use, the reliance on opioids for the treatment of pain has in

part lead to the opioid crisis of the past 2 decades. New model systems are necessary to identify alternative analgesics which combine efficient pain management, but with limited dependency. To address this, we developed the Pain-in-a-Dish Assay (PIDA), a system leveraging human iPSC-derived nociceptors (RealDRG™, Anatomic, Inc) with Vala Sciences' IC200 Kinetic Image Cytometer (KIC®) for high-throughput functional analysis. To demonstrate modulation of nociceptor activity, we treated RealDRG™ neurons with agonists and antagonists of specific ion channels relevant to pain sensation. For functional assays, the RealDRG™ neurons are plated on imaging quality 96-well dishes and cultured for two to three weeks prior to being loaded with hoechst for detection of nuclei and a fluorescent calcium dye. In imaging buffer, cultures are pre-treated with antagonists of channel activity or inert vehicle controls, and calcium videos are acquired on the IC200-KIC at 4 Hz. After one minute of baseline activity, agonists are dispensed into the culture while the KIC continues to capture the agonist-induced changes in calcium activity for two more minutes. We detected a clear dose-dependent response in both somas and neurites after treatment of RealDRG's with the sodium channel agonist, Veratridine (VTD). We also detected increased activity in the somas and neurites after addition of Nav1.7 agonist OD1 and K⁺ channel antagonist 4-aminopyridine (4-AP). Pre-incubation with GX-201, a Nav1.7 antagonist, led to dose-dependent decrease in the max and mean amplitudes and rise time of both soma and neurite VTD-induced responses. Pre-incubation with tetrodotoxin (TTX), an antagonist of voltage gated sodium channels, led to more modest effects, with inhibition of the VTD-induced response speed but not amplitude. This result suggests the presence of TTX-independent channels in the cells. Collectively this data suggests that targeting DRG ion channels is an attractive avenue for discovering new therapeutics for modulating DRG function and ultimately the mitigation of pain.

Disclosures: S.K. Gilmore-Hall: None. C.G. Rines: None. L. Harrison: None. A. Smith: None. K.L. Gordon: None. V. Truong: None. P. Walsh: None. B. Tekwani: None. J. Price: None. P. McDonough: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.14/I4

Topic: E.01. Somatosensation – Pain and Itch

Support: 1RM1NS128741
1R61AT012284

Title: Evaluating novel biomarkers and patient characteristics to predict the efficacy of interventional pain procedures

Authors: *L. E. SAMS¹, E. DING¹, A. KUMAR¹, A. MCDERMOTT¹, E. LUO², J. OKONKWO³, Z. A. CURRY¹, G. J. BRENNER¹, D. HAO¹, A. MUELLER¹, M. L. LOGGIA², B. J. WAINGER³;

¹Dept. of Anesthesia, Critical Care, and Pain Med., Massachusetts Gen. Hosp., Boston, MA;
²Dept. of Radiology, Massachusetts Gen. Hosp., Charlestown, MA; ³Dept. of Neurol.,
Massachusetts Gen. Hosp., Boston, MA

Abstract: There are numerous interventional procedures for different pain conditions, yet the evidence supporting the efficacy of such procedures for chronic pain remains limited. Relatedly, the selection of patients for such procedures is based largely on clinical judgement instead of established predictors of efficacy. The potential of studying patient-related factors, ranging from psychosocial aspects such as catastrophizing to high baseline pain scores, has emerged as a promising avenue to predict procedural efficacy and patient response. Our study uses real-world data on patient-reported outcomes (PROs) before and after interventional pain procedures to identify demographic, clinical, and biological features that predict positive outcomes in defined subsets of pain patients. Data is collected through an observational cohort study of approximately 200 individuals undergoing treatment for chronic pain at the Massachusetts General Hospital Pain Management Center. The study population includes all interested patients over the age of 18 who are under consideration for an interventional pain procedure (e.g. epidural steroid injection), regardless of whether they ultimately elect to receive the procedure. Participants complete a series of questionnaires selected from the NIH's HEAL Initiative Common Data Element repository, assessing their pain characteristics, mood, and sleep before their procedure and at five follow-up time points over the course of six months. A novel tablet-based pain-mapping software is used to assess baseline pain widespreadness (PW), defined as the proportion of the body the participant indicates as painful. In a subset of participants, wearables measuring digital biomarkers, from physical activity to electrodermal activity, is administered for one week pre- and post-procedure. Baseline PW is validated through multiple linear regression analysis predicting PW from baseline Pain Catastrophizing Scale (PCS) scores while controlling for pain intensity, pain interference, depression, anxiety, age, sex, medications, and the recommended procedure. A separate linear regression analysis is used to predict procedure efficacy related to overall pain and general activity at each time point after the intervention, with age, sex, procedure type, baseline pain intensity and interference included as covariates. Through this study, we hope to identify biomarkers and pain profiles which can be assessed prior to an interventional procedure and predict positive outcomes, ultimately improving patient selection for chronic pain interventions.

Disclosures: L.E. Sams: None. E. Ding: None. A. Kumar: None. A. McDermott: None. E. Luo: None. J. Okonkwo: None. Z.A. Curry: None. G.J. Brenner: None. D. Hao: None. A. Mueller: None. M.L. Loggia: None. B.J. Wainger: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.15/15

Topic: E.01. Somatosensation – Pain and Itch

Support: NCCIM Grant R01AT009693

Title: Neural mechanisms supporting mindfulness-based modulation of evoked chronic low back pain: a perfusion fMRI study

Authors: *M. GIANOLA¹, J. G. DEAN², V. OLIVA¹, G. RIEGNER³, L. KHATIB³, D. BARROWS³, A. D. JACOBSON⁴, T. LIU⁵, F. ZEIDAN⁶;

¹Anesthesiol., Univ. of California San Diego, La Jolla, CA; ²Anesthesiol., ³UCSD, San Diego, CA; ⁴San Diego State Univ., San Diego, CA; ⁵Univ. California San Diego, La Jolla, CA;

⁶Anesthesiol., UC San Diego, La Jolla, CA

Abstract: Chronic low back pain (cLBP) is the primary cause of disability¹. Mindfulness meditation (MM), performed by sustained non-reactive attention to the present moment, reduces experimental and chronic pain^{2,3}. However, clinical utility remains limited due to a lack of mechanistic data specific to cLBP and differentiation from appropriate active controls. In healthy individuals, MM reduces pain via decreased default mode network (DMN) and increased orbitofrontal cortex (OFC) activity, possibly reflecting top-down regulation of nociception^{4,5}. To assess if said mechanisms translate to cLBP, 99 patients with cLBP completed all study procedures. Psychophysical pain ratings were collected using a numerical rating scale (0= “no pain”, 10= “worst pain imaginable”) in response to the radicular cLBP evoking straight leg raise test (SLR). Multiphase pulsed continuous arterial spin labeling fMRI (TE=3.3ms; TR=2550ms; 60×2.4mm slices) was acquired before and after randomization to one of three 6-session interventions: 1) MM (n=33; non-reactive focused attention on breath), 2) sham mindfulness meditation (SMM; n=31; slow-paced breathing), or 3) book-listening control (n=35; *Natural History of Selborne*). We hypothesized (NCT03354585) that 1) MM would produce greater analgesia compared to SMM and the control group and 2) MM-based analgesia would be associated with greater OFC activation and DMN deactivation. During the post-intervention fMRI, the SLR was performed across all patients during rest. A second SLR was administered after which the MM and SMM groups engaged in meditation, and the control group rested. DMN and OFC regions of interest were defined to measure changes in cerebral blood flow (CBF) across groups and conditions (meditation vs rest). Pain ratings and CBF in DMN and OFC were treated as outcomes in linear mixed models to test behavioral and mechanistic hypotheses, respectively. MM (b=-0.82, p<.01) and SMM (b=-0.69, p=.02) significantly reduced SLR-evoked pain compared to controls (b=-0.31, p=.11). MM (b=-4.74, p<.01) and SMM (b=-3.77, p=.02) significantly reduced CBF in the OFC and DMN (MM: b=-2.55, p=.04; SMM: b=-3.47, p<.01) as compared to the controls. However, MM-based pain relief was driven by greater OFC (b=0.09, p=.01) and DMN (b=0.08, p=.02) deactivations. SMM-based analgesia was not associated with these mechanisms (OFC: b=.02, p=.50; DMN: b=-0.01, p=.90). Changes in DMN (b=0.04, p=.61) and OFC (b=0.05, p=.17) did not predict pain ratings in the control group. We provide novel evidence that MM reduces evoked cLBP by attenuating activity in self-referential and appraisal systems, reflecting a novel pain modulatory brain mechanism.

Disclosures: M. Gianola: None. J.G. Dean: None. V. Oliva: None. G. Riegner: None. L. Khatib: None. D. Barrows: None. A.D. Jacobson: None. T. Liu: None. F. Zeidan: None.

Poster

PSTR022: Human Pain Mechanisms and Models

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR022.16/I6

Topic: E.01. Somatosensation – Pain and Itch

Support: Veterans Affairs 1 I21RX004410-01 A1
NIH/NIBIB P41 EB018783

Title: Bilateral Proximal Lower-Limb Cutaneous Reflexes in Healthy Controls and People with Amputations

Authors: S. RUEDA-PARRA¹, R. L. HARDESTY, Jr.², J. R. WOLPAW³, *J. A. BRANGACCIO⁴;

¹Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; ²Res., Natl. Ctr. for Adaptive Neurotechnologies, Sauquoit, PA; ³Natl. Ctr. for Adaptive Neurotechnologies, Natl. Ctr. for Adaptive Neurotechnologies, Delmar, NY; ⁴NCAN@Stratton VA Med. Ctr., Albany, NY

Abstract: Introduction H-reflex operant conditioning (HROC) is a new therapy that produces beneficial plasticity in spinal reflex pathways (doi: 10.3389/fnint.2014.00025). We aim to translate this strategy to the cutaneous reflexes (CRs). CRs contribute to motor control (e.g., posture, locomotion, and balance) and sensory processing (e.g. light touch and pain), making them promising targets for treating chronic pain such as phantom limb pain (PLP). PLP is driven by altered sensory processing after amputation. However, little is known about CRs in the residual limb after amputation. To date, most work has studied distal CRs (e.g. sural nerve) in healthy populations. Although recent work by Phipps et al. showed successful conditioning of distal CRs and reduced pain in a person with spinal cord injury, distal sites are not accessible after amputation. Thus, we tested an alternative stimulation (stim) site to evoke CRs, with the long-term goal of developing an operant conditioning therapy to reduce PLP and improve balance. **Methods** We adapted our HROC protocol to elicit CRs in proximal leg muscles by stimulating the saphenous nerve. CRs were recorded from the *rectus* or *biceps femoris*, based on available musculature and control. Responses were elicited bilaterally in 15 healthy controls (HC) and 4 people with lower-limb amputation. Stim intensities were normalized using 3 perceptual thresholds: (1) detection (first sensation), (2) radiating (sensation beyond the site), and (3) discomfort (i.e. pain). Five stim levels were defined relative to the difference between radiating and pain thresholds: -25%, 25%, 50%, 75%, and 100% (30 trials at each level, starting with the dominant limb). Prestimulus EMG (-100 to -10 ms) was subtracted, and the first positive response peak in the average response at each level was analyzed. **Results** We were able to elicit CRs in HCs and people with above-knee or below knee amputation. CR size grew with stim intensity; it appeared at 25-75% and changed little from 75% to 100% (i.e., pain). CR size differed between right and left legs in both HCs and people with amputations. The latter had diminished CRs in the residual limb. In several HCs in whom the CR was up-conditioned over sessions, detection and radiating thresholds did not change, while pain threshold rose gradually. **Conclusions** We have developed a protocol for operant conditioning CRs in people with amputations. In several HCs studied to date, this conditioning has increased the pain threshold.

These initial results indicate that CR operant conditioning could be applied in people with amputations, and suggest that it might possibly be able to reduce PLP.

Disclosures: S. Rueda-Parra: None. R.L. Hardesty: None. J.R. Wolpaw: None. J.A. Brangaccio: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.01/I7

Topic: E.04. Interoception

Support: Ministry of Science and Technology (MOST) grant 109-2628-B-001-013

Title: Pickpocket channels mediate osmosensing in a pair of thirst neurons in *Drosophila*

Authors: *C.-T. LIN^{1,2}, B. SENAPATI^{1,3}, S. LIN¹;

¹Inst. of Mol. Biology, Academia Sinica, Taipei, Taiwan; ²Mol. and Cell Biology, Taiwan Intl. Grad. Program, Academia Sinica and Natl. Def. Med. Ctr., Taipei, Taiwan; ³Ctr. for Neural Circuits and Behavior, Univ. of Oxford, Oxford, United Kingdom

Abstract: Thirst is an essential survival drive triggered by dehydration. It motivates animals to seek and consume water to restore body fluid homeostasis. In mammals, neurons in the subfornical organ (SFO) and organum vasculosum lamina terminalis (OVLT) detect increased blood osmolality, a hallmark of dehydration, and trigger thirst-driven behaviors. In invertebrates, we previously identified a pair of leucokinin-expressing neurons (LHLKs) in the *Drosophila* brain that regulate thirst-driven behaviors and are activated by extracellular hyperosmolality. How do these neurons sense the elevated osmolality? Recent studies have identified TMEM63B as a candidate osmosensor in excitatory SFO neurons in mammals. However, the osmosensor and neural mechanism in invertebrates remain largely unknown. Removal of the fly ortholog of TMEM63B did not affect LHLKs' responses, suggesting that flies may rely on a distinct molecule to sense hyperosmolality. Here, we demonstrated, using calcium imaging, that LHLKs respond directly to hyperosmotic stress. Their responses scale with osmolality, suggesting that LHLKs can encode graded levels of dehydration. Notably, LHLKs' activities under hypertonic conditions correlate with cell body shrinkage, supporting the idea that osmosensing involves mechanosensors detecting membrane tension. We screened candidate mechanosensitive ion channels using RNAi and behavioral assay and identified Pickpocket 26 (PPK26), a fly ortholog of DEG/ENaC/ASIC channels, as a putative osmosensor. Knockdown of *ppk26* in LHLKs impairs water-seeking behavior and reduces hypertonicity-induced responses. Since PPKs typically form complexes, we also identified RPK, another member of the PPK family, as a potential partner of PPK26. Loss of RPK impairs LHLKs' responses to hypertonicity and water-seeking behavior. As LHLKs show sustained calcium activity under high osmolality—possibly reflecting ongoing thirst—we asked how this activity is maintained. We found that osmosensory

responses in LHLKs require external Ca^{2+} influx and are sustained by Cav2 voltage-gated calcium channels. Blocking Cav2 with PLTX-II diminishes persistent activity without affecting the initial response. Together, we identify the PPK26/RPK complex as a novel osmosensor crucial for thirst sensing in flies and reveal a potential osmosensing mechanism. Given the evolutionary conservation of DEG/ENaC/ASIC channels, these channels may also function as additional osmosensors in mammals alongside TMEM63B. This work broadens our understanding of how the brain senses and responds to dehydration across animal species.

Disclosures: C. Lin: None. B. Senapati: None. S. Lin: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.02/I8

Topic: E.04. Interoception

Support: NIH R01MH128398
Ronald F. and Janice A. Zollo Fellowship, CMU College of Engineering

Title: An interoceptive role for respiration in behavior and neural activity in non-human primates

Authors: *E. E. SKOG;
Biomed. Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Interoception, the brain's capacity to sense and integrate internal physiological states, has emerged as a key component in cognition, behavior, and emotional regulation. Among the different internal rhythms, respiration is increasingly recognized not merely as a passive background process but as a modulator of perception and decision-making. In this study, we investigate how spontaneous breathing entrains to a visual discrimination task and shapes behavior in non-human primates (NHPs). One male rhesus macaque performed a color change detection task while respiration was continuously monitored via a thermocouple. We extracted respiratory features (e.g., timing, depth, volume, phase) from 41 sessions. A total of 11 interpretable features were derived using peak detection, signal integration, and the Hilbert transform. We found that there were significant differences for a multitude of features between correct and incorrect trials, mostly for features related to timing and phase in respect to trial onset. Finally, all features were used to classify trial outcomes (correct, incorrect) using multiple machine learning models. A boosted random forest classifier achieved above chance performance (~74% cross-validated accuracy) across both five-fold and leave-one-session-out validations, highlighting the predictive value of respiratory dynamics for trial-by-trial behavior. Additionally, we measured visual cortical activity in areas V1 and V4 with two 64-channel intracortical electrode "Utah" arrays. We measured local field potentials (LFPs) and decomposed the LFP signal into power in frequency bands aligned to inhalation onset. We found enhanced

power at the time of inhalation, particularly in the alpha, beta and gamma frequency bands. This task-locked neural entrainment suggests a close interaction between respiration and cortical excitability, although it remains to be determined whether this coupling is behaviorally driven, respiration-driven, or driven by a common latent process. Together, our results demonstrate that respiration is both aligned with neural activity and behavioral task performance, consistent with an interoceptive role in neurons and behavior.

Disclosures: E.E. Skog: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.03/I9

Topic: E.04. Interoception

Support: Boehringer Ingelheim Fonds PhD Fellowship
 Duke Institute for Brain Sciences Incubator Award

Title: Decoding neural responses to gut-mediated signals in larval zebrafish

Authors: *M. ARINEL¹, J. A. ATKINSON¹, K. MATOS¹, E. P. DRAGE¹, M. HAWKYARD², E. A. NAUMANN¹;

¹Neurobio., Duke Univ., Durham, NC; ²Univ. of Maine, Orono, ME

Abstract: Animals must rapidly sense the quantity and quality of ingested food to regulate feeding behaviors essential for survival. Enteroendocrine cells (EECs) in the gut epithelium detect distension and nutrients and rapidly signal the brain via synaptic connections with vagal neurons. However, how these mechanosensory and chemosensory gut signals are encoded by the nervous system remains poorly understood, particularly at early developmental stages. Here, we leveraged the optical transparency and genetic accessibility of larval zebrafish to uncover the neural encoding of gut-derived signals. To investigate how different nutrients in the gut influence behavior, we developed a gut-mediated feeding assay. Using odorless alginate particles to encapsulate specific nutrients, we assessed how gut-derived chemical signals affect feeding in freely swimming larvae. Glycine robustly stimulated feeding, whereas glucose, which is typically rewarding for mammals, had no such effect. Interestingly, EEC-depleted fish increased their nutrient-specific intake of glucose and glycine, but not control stimuli, indicating that EECs contribute nutrient-specific satiety signals. To then understand how these post-consummatory gut signals are neurally encoded, we developed a novel microgavage technique that enables precise delivery of ecologically relevant stimuli directly into the gut of intact, awake larvae. Combined with two-photon calcium imaging, this approach allowed us to monitor vagal and hindbrain neural responses to defined gut stimuli at single-cell resolution. We found that mechanical stretch of the gut robustly and rapidly activates and suppresses neuronal populations across the vagus and dorsal hindbrain. These widespread responses to stretch identify gut distension as the

dominant visceral cue at this developmental stage. Introducing chemical stimuli alongside gut stretch revealed nuanced neural response dynamics. While nutritive stimuli did not significantly alter neural responses compared to stretch alone, aversive allyl isothiocyanate (AITC) uniquely elicited delayed neural dynamics. This underscores the importance of temporal coding within gut-brain communication and suggests a distinct encoding mechanism for aversive gut stimuli at the level of the vagus and hindbrain. These results position larval zebrafish as an ideal model for uncovering fundamental principles of gut-brain signaling. Together, our findings illuminate how the gut rapidly communicates both quantity and quality of ingested food to the brain early in development, highlighting its fundamental necessity for survival.

Disclosures: M. Arinel: None. J.A. Atkinson: None. K. Matos: None. E.P. Drage: None. M. Hawkyard: None. E.A. Naumann: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.04/I10

Topic: E.04. Interoception

Title: Resting-state spectral power markers of insular dysregulation in suicide attempt history

Authors: *B. H. CHANDLER, C. R. CORTES, B. D. GREENE, A. FIJTMAN, H. HU, C. A. ZARATE, Jr., E. D. BALLARD, J. R. GILBERT;

Exptl. Therapeut. and Pathophysiology Br., Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Background: Altered insular activity is implicated in major depressive disorder (MDD) and suicidal ideation (SI). Recent magnetoencephalographic (MEG) studies have shown increased delta and decreased gamma power in the insula of individuals with SI, while convergent fMRI evidence suggests the insula may play a key role in converting suicidal thoughts into behaviors. One important function of the insula is interoception—a multidimensional construct comprising abilities to sense and relate with internal bodily signals—motivating investigation of how insular neural activity relates to interoceptive processing in suicide attempters.

Our preliminary results suggest a negative relationship between SI and both Self-Regulation (SR) and Trusting (TR) subscales of the Multidimensional Assessment of Interoceptive Awareness (MAIA). However, whether oscillatory power changes in the insula can distinguish suicide attempt history, and how they relate to interoceptive subdomains, is unknown. Therefore, we sought to investigate the relationships between SR and TR subscale scores of the MAIA, resting-state MEG power changes, and suicide attempt history.

Methods: Using a 275-channel CTF system, we acquired one to two resting-state MEG datasets from 37 individuals diagnosed with MDD, grouped by those with (n = 13) and without (n = 24) history of suicide attempts. Source-localized power was computed across canonical frequency bands (delta to high gamma) using synthetic aperture magnetometry. Linear Mixed Effects

modeling in AFNI was used to calculate the relationship between source-localized power, MAIA subscales for SR and TR, and history of suicide attempts.

Results: There were significant group-by-MAIA TR subscale interactions in the anterior insula in delta and theta frequencies. Probing the interactions, attempters were found to have significantly ($p_{FDR} < 0.05$) greater negative relationships between their TR subscale score and MEG power in both frequencies compared to non-attempters. This was part of a larger cluster that included left caudate, left amygdala, left fusiform, left BA24/25, and bilateral hippocampus and precuneus.

Conclusions: Our findings replicate and extend evidence that resting-state insular spectral power alterations are putative markers of suicidality. Furthermore, altered associations between interoceptive self-reports and neural oscillations highlight potential mechanisms of interoceptive dysregulation in suicidal states. These results support the utility of insular spectral profiles as potential biomarkers for suicide risk stratification and targets for intervention.

Disclosures: **B.H. Chandler:** None. **C.R. Cortes:** None. **B.D. Greene:** None. **A. Fijtman:** None. **H. Hu:** None. **C.A. Zarate:** None. **E.D. Ballard:** None. **J.R. Gilbert:** None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.05/I11

Topic: E.04. Interoception

Support: Wellcome Trust

Title: Sensing your own heartbeat: neural basis of cardiac interception using fMRI

Authors: ***S. KUMAR**¹, J. S. WINSTON², J. I. BERGER¹, M. I. BANKS³, K. V. NOURSKI¹, M. ZANATY¹, M. A. HOWARD, III¹, T. D. GRIFFITHS⁴;

¹Univ. of Iowa, Iowa City, IA; ²Kings Col. London, London, United Kingdom; ³Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI; ⁴Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: There has been a growing interest in interoception which concerns perception of internal body state. A typical task used as a marker of interoception is the heartbeat counting task in which participants are asked to count their own heartbeat over a chosen time interval. The reported count is then compared with the actual number of recorded heartbeats to assess the accuracy of heartbeat perception. In addition to behavioral studies, this task has also been used in some neuroimaging studies to determine the brain network underlying heartbeat perception. However, one limitation of these studies is frequently the absence of a good control task. It is known that counting of own heartbeats is challenging with only 40% of people getting a score of 80% or above. To delineate brain network that is specific to interoception, a control exteroceptive task is needed which is matched in difficulty and performance. In the current work

we developed such a control visual task in which participants count visual targets (visual target counting, VTC) or count their own heartbeats (heartbeat counting, HBC). During the VTC, participants count visual targets (Gabor patches at 45 degrees) embedded in a 10Hz visual stream comprising noise and distractors (Gabor patches at -45 degrees) whereas they count their own heartbeats in the HBC task over matched time periods. Most importantly, visual targets, noise and distractors are continuously displayed when the participant is engaged in counting heartbeats. This way participants are required to shift attention to the relevant modality with the sensory input for visual and interoceptive signals being continuously received. Twenty healthy participants performed this task inside a 3T MRI scanner while undergoing BOLD fMRI. Behavioral data showed that (i) accuracy [HBC: 75.2% (19.28); VTC: 81.7% (11.81)] was not significantly different between the two tasks (ii) HBC accuracy was negatively correlated ($r = -0.72$, $p < 0.001$) with variability in heart rate indicating high performance in HBC is associated with a more stable heart rate during the task. fMRI data showed stronger activity in the anterior and posterior insula bilaterally and anterior cingulate during the HBC task compared to VTC. Functional connectivity of anterior insula to the rest of brain showed significant positive correlation with posterior insula and negative correlation with occipital cortex suggesting 'boosting' of cardiac and 'inhibition' of competitive visual information while counting heartbeats. Our results suggest that anterior insula is not only activated when attending to interoceptive signals but may also regulate flow of distracting sensory exteroceptive signals.

Disclosures: S. Kumar: None. J.S. Winston: None. J.I. Berger: None. M.I. Banks: None. K.V. Nourski: None. M. Zanaty: None. M.A. Howard: None. T.D. Griffiths: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.06/I12

Topic: E.04. Interoception

Support: Graduate School, The University of Hong Kong

Title: Updated Evidence in Relating Cardiac Interception Task and EEG indices: A Systematic Review

Authors: *C. X. LI, W. ZHAO, Z. MU, R. HO;
The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Background: Cardiac interoception refers to the process of sensing, storing, and representing information regarding the state of the cardiovascular system. This ability is considered to play a vital role in emotional processing, perception, and self-awareness. Behavioural tasks and self-report questionnaires are commonly employed to assess cardiac interoceptive ability; however, these methods have significant limitations, particularly regarding their applicability to specific populations and the inherent prediction errors that can arise during

experiments. Consequently, electroencephalography (EEG), a neuroimaging technique capable of capturing instantaneous brain dynamics, has been increasingly utilised to explore the potential for measuring cardiac interoceptive ability. **Methods:** A systematic review was conducted to synthesize the present English-written peer-reviewed journal papers of electroencephalogram (EEG) studies of cardiac interception across five databases (Pubmed, Embase, MEDLINE, Web of Science, and PsycINFO). The standardized assessment criteria developed by Kmet and colleagues was used for the assessment for risk of bias. **Results:** Among 3425 records identified from the selected database, 21 studies met the inclusion criteria. The cardiac interoceptive tasks—Heartbeat Counting Task (also called Heartbeat Tracking Task, Heartbeat Detecting Task, Heartbeat Perception Task), Heartbeat Discrimination Task (also called Heartbeat Detection Task), Heartbeat Detection Task (also called Heartbeat Perception Task)—assess cardiac interoceptive accuracy (IA), sensibility (IS), and metacognitive awareness (IM). IA, the most studied measure, correlates significantly with spectral alpha power, gamma oscillations, and auditory-evoked N1 potentials but not with P2 components or stimulus-preceding negativity (SPN). Heartbeat-evoked potentials (HEP), a common neural marker for IA, yield inconsistent findings: nine studies report significant IA-HEP associations, while nine others find none. IS has only been examined with HEP, showing no significant differences among sensible or unsensible perceivers. One study found a significant IS-HEP correlation, but this was not replicated. For IM, one study reported a significant link with gamma phase synchrony but not with HEP. **Conclusions:** The present study reviewed current knowledge regarding the application of EEG indices for cardiac interception. This knowledge provides insights and direction for future research on the use of EEG indices in related fields.

Disclosures: C.X. Li: None. W. Zhao: None. Z. Mu: None. R. Ho: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.07/J1

Topic: E.04. Interoception

Support: NIH R01 DC004290

Title: Heartbeat Processing and Cardiac-Phase Dependent Modulation of Sound Responses in the Human Insula and Auditory Cortex at the Single-Neuron Level

Authors: *G. SHARMA¹, J. I. BERGER¹, J. S. WINSTON³, P. E. GANDER², H. D. CRITCHLEY⁴, M. A. HOWARD, III¹, S. KUMAR¹, M. ZANATY¹;

¹Dept. of Neurosurg., ²Dept. of Radiology, Univ. of Iowa, Iowa City, IA; ³King's Col. London, London, United Kingdom; ⁴Univ. of Sussex, Brighton, United Kingdom

Abstract: There has been an increasing interest in interoception, the perception of internal bodily signals, due to its significant impact on various cognitive, affective functions, and

psychiatric disorders. A large body of evidence from humans using fMRI, EEG and MEG, as well as neurophysiology in animals, shows that the insula, also referred to as the primary interoceptive cortex, is a key brain region for processing interoceptive signals from the body. However, because of the limited spatial (EEG/MEG) and temporal (fMRI) resolution of the noninvasive methods, precise spatiotemporal dynamics of the insula in processing interoceptive signals in humans remain unknown. In the current work, we measured responses to cardiac beats in the human insula at the single-unit level, which, to the best of our knowledge, is the first study to record interoceptive neural activity at such a high spatial-temporal resolution in humans. Another important question concerns interactions between interoception and exteroception (perception of signals from the outside world, e.g. auditory). A popular idea developed particularly for cardiac interoception more than 50 years ago is the ‘baroreceptor hypothesis’ (Lacey and Lacey, 1978), which states that processing of exteroceptive signals in the sensory cortex during the systole phase of the cardiac cycle is inhibited. We tested this hypothesis by recording single-unit activity (SUA) in the primary auditory cortex (Heschl’s gyrus, HG) in response to sounds presented during the systole and diastole phases of the cardiac cycle. SUA was recorded using Behnke Fried depth electrodes from ten adult human participants with intractable epilepsy. These participants were implanted with intracranial electrodes to localize their seizure focus. Participants passively listened to a series of tones (duration = 300 ms, inter-stimulus interval = 2 seconds) ranging from 0.25 to 8 kHz in 1-octave steps. The results showed that 6% of neurons in the posterior insula (mean latency = 230ms), 5% in the anterior insula (mean latency 260ms) and 9% in the HG (mean latency = 370ms) responded to heartbeats. Analysis of modulation of sound response with cardiac phase showed that a total of 7% of sound-responsive neurons in the HG showed a significantly lower firing rate in the systole compared to the diastole phase, indicating the inhibition of the auditory cortex during systole, which is consistent with the baroreceptor hypothesis. In summary, our data shows that cardiac signals are represented both in the insula and auditory cortex and that sound responses in the primary auditory cortex are modulated by the cardiac phase.

Disclosures: G. Sharma: None. J.I. Berger: None. J.S. Winston: None. P.E. Gander: None. H.D. Critchley: None. M.A. Howard: None. S. Kumar: None. M. Zanaty: None.

Poster

PSTR023: Interoception Across Species

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR023.08/J2

Topic: E.04. Interoception

Support: R01HL163578

Title: Mapping the cortical basis of respiratory interoception using intracranial EEG

Authors: *J. Y. ASSI^{1,2}, S. BICKEL², H. GREENBERG³, N. MESGARANI⁴, A. D. MEHTA⁵, J. HERRERO RUBIO²;

¹Univ. of Cincinnati Col. of Med., Cincinnati, OH; ²Neurosurg. - Neurol., Feinstein Inst., Manhasset, NY; ³Sleep Medicine, Pulmonology, Northwell, Manhasset, NY; ⁴Columbia Univ., New York, NY; ⁵Neurosurg., Hofstra Northwell Sch. of Med., Manhasset, NY

Abstract: How does the human brain detect disruptions in breathing? While animal models have clarified brainstem control of respiration, many human breathing disorders involve impaired cortical interoceptive processing. To investigate this, we recorded intracranial EEG (iEEG) from 12 epilepsy patients performing a breathing task with brief, randomly timed 300 ms inspiratory occlusions. Occlusions evoked robust high-frequency activity (HFA) responses in insular, sensorimotor, and orbitofrontal cortices. The somatosensory cortex showed the earliest (~80 ms) and strongest (>20% ΔHFA) responses, with later engagement (~300-400 ms) of orbitofrontal and posterior insular areas. HFA responses were positively correlated with respiratory effort (indexed by mouth pressure) in the posterior insula and somatosensory cortices, and negatively correlated in orbitofrontal and motor cortices, suggesting region-specific encoding of respiratory sensations. These findings define a distributed cortical network for detecting and responding to airway occlusion and highlight potential neural markers of the human drive to breathe. This work informs future efforts to map the cortical basis of respiratory interoception and dyspnea.

Disclosures: J.Y. Assi: None. S. Bickel: None. H. Greenberg: None. N. Mesgarani: None. A.D. Mehta: None. J. Herrero Rubio: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.01/J3

Topic: E.05. Auditory and Vestibular Systems

Title: Sensitivity to jerk self-motion in the macaque vestibular cortices

Authors: *J. SHAN, Y. GU;
Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China

Abstract: Vestibular system is critical for many cognitive and motor functions by detecting acceleration and velocity of self-motion in the environment. Concordant with this, vestibular signals have been shown to present plentiful temporal dynamics in many sensory cortices, indicating they may be involved in different functions. However, in previous studies, the exact temporal dynamics have been measured in limited experimental conditions which have confounded their ground truth. Here we examined temporal dynamics of vestibular signals of single neurons in three vestibular areas, including the parieto-insular vestibular cortex (PIVC), the ventral intraparietal area (VIP), and the medial superior temporal area (MST), when macaques are linear-translated by a six-degree-of-freedom motion platform. We designed new kinematic profiles (e.g., velocity, acceleration, and jerk) to be able to dissociate from each temporal component. Contrary to prior reports showing much acceleration or velocity coding, we

found that the new paradigm revealed predominant jerk signals in all areas. A direct comparison between previous and current methods indicated that many acceleration signals measured in traditional ways were actually jerk response. Our findings indicate that the jerk signals are widely distributed in the vestibular sensory cortices, which may be important for transient detection of self-motion or motor control in the environment.

Disclosures: J. Shan: None. Y. Gu: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.02/J4

Topic: E.05. Auditory and Vestibular Systems

Support: FA9550-24-1-0300

Title: The neural computation of vestibular illusions

Authors: *J. CARRIOT, I. MACKROUS, M. J. CHACRON;
McGill Univ., Montreal, QC, Canada

Abstract: Pilots often suffer spatial disorientation when visual cues are sparse; most notably, the somatogravic illusion during take-off causes the linear acceleration sensed by the otolith organs to be misread as a nose-up tilt, leading to over-pitching and potential crashes. It is thought that this failure stems from the vestibular system's inherent tilt-translation ambiguity—otoliths cannot distinguish gravity from inertial acceleration. However, the neural correlates of spatial disorientation in the brain remain unknown to date. We addressed this gap by extracellularly recording single-unit activity from vestibular neurons in behaving non-human primates while delivering (i) linear translations, (ii) static and dynamic tilts, and (iii) centrifugation paradigms that mimic the sustained forward acceleration experienced during take-off. Although overall neural responses were highly heterogeneous, we discovered a distinct sub-population whose firing rates remained low during translation alone but rose sharply—and in temporal lockstep with the animals' report of illusory nose-up tilt—when identical linear accelerations were applied under centrifugation. Indeed, mathematical models including tuning to the perceived tilt could successfully predict changes in neural activity. These “illusion-tuned” vestibular neurons therefore provide the first direct neural correlate of the somatogravic illusion in the brain and highlight a dedicated channel through which ambiguous otolith signals are misinterpreted as changes in orientation relative to gravity.

Disclosures: J. Carriot: None. I. Mackrous: None. M.J. Chacron: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.03/J5

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01-DC002390
R01-DC018061
1UF1NS111695-01
CIHR

Title: Spike timing precision improves stimulus detectability by central vestibular neurons

Authors: I. MACKROUS¹, J. CARRIOT¹, K. E. CULLEN², *M. J. CHACRON¹;
¹McGill Univ., Montreal, QC, Canada; ²Dept. of Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: Perceptual detection thresholds for self-motion, sound, and light often approach the limits set by environmental noise, yet detection thresholds based on neural activity (i.e., “neurometric”) derived from single-unit firing-rate changes are typically an order of magnitude higher. This long-standing discrepancy raises the possibility that behavioral sensitivity is obtained by considering other attributes of neural activity than firing rate. While spike timing can in theory carry much more information than firing rate, this attribute has not been explicitly considered when computing neurometric detection thresholds. We recorded single vestibular nuclei (VN) neurons in two rhesus macaques during translational or rotational stimuli delivered by a motion platform. For each neuron we computed detection thresholds using two Signal Detection Theory metrics: (i) traditional rate-based d' and (ii) d' computed from the VanRossum distance between repetition of the same stimuli to capture millisecond-scale temporal patterns. Rate-based neurometric thresholds were $\sim 6 \times$ higher than psychophysical thresholds found in human subjects. Strikingly, thresholds computed from distance metrics yielded a large reduction of the thresholds when considering short timescales, producing neurometric values that are more similar to perceptual ones. Mathematical modeling and computational data analysis revealed that spike timing precision accounted for observed differences. Our findings demonstrate that temporal precision, rather than average firing rate, can reconcile single-unit sensitivity with perceptual performance. Because similar millisecond-level synchrony has been reported across sensory modalities, incorporating the fine structure of spiking activity into quantification of neurometric detection thresholds may be essential for understanding how small neuronal populations achieve near-behavioural acuity.

Disclosures: I. Mackrous: None. J. Carriot: None. K.E. Cullen: None. M.J. Chacron: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.04/J6

Topic: E.05. Auditory and Vestibular Systems

Support: Johns Hopkins Discovery Grant
IRACDA K12 - GM123914

Title: Processing of self-motion in the vestibular nuclei of mice

Authors: *M. L. S. GREEN^{1,2}, B. M. VERDONE¹, J. CARRIOT², M. J. CHACRON², K. E. CULLEN¹;

¹Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; ²Physiol., McGill Univ., Montreal, QC, Canada

Abstract: Understanding how the brain encodes and processes self-motion and spatial orientation is a central question in sensory neuroscience. The vestibular system plays a crucial role in this process, transmitting signals from sensory organs in the inner ear through an ascending neural pathway including the brainstem, thalamus, and cortex. While traditionally considered linear, recent studies in non-human primates reveal that vestibular neurons exhibit nonlinear responses. However, the mechanisms underlying these nonlinearities and their role in population coding remain unclear. Mice offer a powerful model for investigating these mechanisms as they can be genetically manipulated to target specific brain regions for study, paired with well-established behavioral paradigms, these advantages allow for them to be a good model for probing the vestibular pathway. However, the vestibular system in mice has not been as extensively studied as in non-human primates. Initially focusing on expanding our understanding of activity in the vestibular nuclei (VN), we recorded neural activity using Neuropixel probes in head-fixed mice subjected to horizontal rotational stimuli delivered via a dynamic custom motion platform. Stimuli included single-sine wave rotations across frequencies (0.5-17 Hz), white noise and complex waveforms combining low and high frequency components (up to 20 Hz), as well as naturalistic motion. Overall, our findings demonstrate that vestibular nuclei (VN) neurons in mice exhibit key functional properties characteristic of medial vestibular nucleus neurons previously described in primates. First, mouse VN neurons exhibit high-pass tuning, with both sensitivity and phase increasing as a function of stimulus frequency. Second, responses to combined stimuli reveal nonlinear interactions—most notably a boosting nonlinearity—such that when low- and high-frequency stimuli are presented concurrently, the interaction produces an intensity-dependent bias in the output firing rate, attenuating sensitivity to low-frequency inputs. Finally, spike timing analyses show that mouse VN neurons employ temporal coding. These findings establish strong parallels between mouse and primate vestibular processing, by revealing conserved features previously established in primates. Building on this foundation, our future work will target thalamic and cortical areas to uncover population dynamics and circuit-level mechanisms. With the added advantage of genetic accessibility, the mouse offers a powerful system for uncovering how the brain encodes self-motion and spatial orientation.

Disclosures: M.L.S. Green: None. B.M. Verdone: None. J. Carriot: None. M.J. Chacron: None. K.E. Cullen: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.05/J7

Topic: E.05. Auditory and Vestibular Systems

Support: St Germain Research endowment to the Department of Otolaryngology at UTMB
Seinsheimer Research endowment to the Department of Otolaryngology at UTMB

Title: Virtual reality controlled by a novel locomotion device to modulate vestibular perception

Authors: *T. MAKISHIMA, R. COOK;
Univ. of Texas Med. Br., Galveston, TX

Abstract: Introduction: Falls result in injuries requiring medical treatment and restrict of basic activities such as standing or walking. Vestibular physical therapy (PT) is effective to improve vestibular function and subsequently preventing fall-related morbidities. However, subjects with vestibular dysfunction may have limited physical mobility in addition to the perception of dizziness which limit their access to traditional PT. Virtual reality (VR), a computer-generated simulation of real or imaginary environments that allows user interactions has been applied to vestibular PT with demonstrated effectiveness. Our goal was to trial VR with a novel locomotion device and test if an assisted standing or sitting position of the body allowing for a different way of controlling movement could effectively stimulate the vestibular system. Methods: Thirty healthy subjects were recruited for this pilot study. Sensory Organization Test on the computerized dynamic posturography and the Simulator Sickness Questionnaire (SSQ) was performed before and after the VR session. The VR stimulus was delivered as a visually and proprioceptively interactive realistic “underground garage” environment through the Meta Quest 2 VR headset and the C-Infinity locomotion device (NeuroSync Laboratories). The subjects explored the underground garage VR content for 3 minutes. The test results before and after VR were compared. Results: SSQ results showed that VR sessions during standing evoked more sickness compared to the sitting position. Posturography results showed that the composite score improved after the VR session. The largest improvement was observed in males after VR in the sitting position. The females with lower scores at baseline improved significantly after VR. Visual and vestibular scores improved after VR. In the visual sensory analysis, there was more improvement after VR in the sitting position. In the vestibular sensory analysis, there was more improvement after VR in the sitting position, especially in male subjects. Overall, the vestibular sensory analysis scores had larger improvement. Conclusion: Our VR setup is safe and effective for the modulation of visual/vestibular perception in healthy subjects both subjectively and objectively. The questionnaire showed subjective improvement in oculomotor perception, albeit with feelings of disorientation. The standing and sitting position seem to induce visual/vestibular stimulation in different intensities. Subjects with poorer balance function at baseline showed greater change in their performance. We hope to further investigate a larger cohort and in patients with vestibular dysfunction.

Disclosures: T. Makishima: None. R. Cook: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.06/Web Only

Topic: E.05. Auditory and Vestibular Systems

Support: NSERC
Chaire Fondation Caroline Durant en audition et vieillissement

Title: Galvanic vestibular stimulation modulates auditory spatial release from masking

Authors: *C. AZAR¹, D. PAROMOV², A. CÉDRAS⁴, M. MAHEU⁵, B.-A. BACON⁶, F. CHAMPOUX³;

¹Univ. de Montréal, Montreal, QC, Canada; ²Audiologie, Univ. de Montréal, Delson, QC, Canada; ³Sch. of speech language pathology and audiology, Univ. de Montréal, Montreal, QC, Canada; ⁴Univ. of Montreal, Longueuil, QC, Canada; ⁵Sch. of Speech Language Pathology and Audiol., Univ. de Montréal, Montreal, QC, Canada; ⁶Psychology, The Univ. of British Columbia, Vancouver, BC, Canada

Abstract: It has been recently suggested that body representation plays a significant role in auditory spatial processing, rendering the processing of auditory cues essentially impossible when the body schema is not accurately updated. Recent evidence also suggests that such errors can be induced through vestibular perturbations, resulting in increased errors in auditory localization. To date, however, no study has explored if these errors are maintained in higher-order auditory spatial processing. This study thus aimed to assess the impact of vestibular perturbations on the spatial release from masking, a process by which the spatial position of auditory objects is exploited to facilitate their segregation from noise. A total of 12 participants were evaluated with the “Masking Level Difference” and the “Listening in Spatialized Noise - Universal” before, during, and after galvanic vestibular stimulation [GVS] (sinusoidal, 2Hz, 1mA). Preliminary data suggest a reduction in spatial release from masking in both tests during GVS, which is recovered once the stimulation is stopped. These results suggest that vestibular inputs, and more so body representation, may play a role in auditory spatial processing that goes beyond auditory localization.

Disclosures: C. Azar: None. D. Paromov: None. A. Cédras: None. M. Maheu: None. B. Bacon: None. F. Champoux: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.07/J8

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant EY036172

Title: Effects of lifetime noise exposure on VOR adaptation

Authors: *A. VELISAR¹, A. VISHT², N. M. SHANIDZE³;

¹The Smith Kettlewell Eye Research Inst., San Francisco, CA; ²The Smith-Kettlewell Eye Res. Inst., Moraga, CA; ³The Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Noise exposure has been implicated in hearing loss and possible damage to the vestibular periphery, although functional studies of vestibular function have shown mixed results. A likely barrier to detection and diagnosis of noise-induced vestibular loss is the difference in susceptibility to noise damage of certain components of the vestibular system. Of the three classes of vestibular afferents, calyx-only afferents exhibit irregular firing rates and phasic responses related to head acceleration. They are also sound sensitive and may thus be susceptible to noise overstimulation. Irregular afferents are also key for VOR gain adaptation. To examine potential effects of noise exposure on VOR adaptation, we tested 7 participants (3M, age: 37-76) with varying degrees of noise exposure. Participants wore an EyeSeeCam Sci binocular eye tracker (250 Hz/eye) and were tested in the dark in 3 conditions: no visual stimulus (VOR), world-fixed visual stimulus (vVOR), and a head-fixed visual stimulus (VOR cancellation). Participants were seated in a chair that rotated in yaw with velocity steps randomized for speed (90 and 120°/s) and direction (CW/CCW). The chair accelerated to a desired angular velocity and rotated for 1 second before slowing down and returning to the initial position. Each participant underwent 60 rotations (15 for each speed and direction). Earth-fixed target placement was optimized to be in participants' field of view during steady state rotation and participants were asked to fixate it as soon as the target became visible. For vVOR cancellation trials, participants were asked to fixate the dot continuously while rotating. In the VOR condition, participants were asked to keep their eyes open and look straight ahead at trial start. Chair and eye signals were synchronized with an IMU mounted to the chair. Head and chair angular velocity was filtered with a fourth order Butterworth low-pass filter (3 Hz cutoff frequency). Blinks and saccades were removed manually. VOR gains were calculated as the ratio of eye and head velocity and averaged across the two eyes. Lifetime noise exposure was assessed using the Noise Exposure Structured Interview (NESI). We did not observe a relationship between VOR gain and noise exposure for any of the conditions ($p > 0.05$, Pearson correlation). There was a significant association between age and VOR responses in the VOR cancellation condition ($R = 0.83$, $p = 0.02$). Our findings may suggest that noise exposure may not affect irregular afferent activity in the semicircular canals. However, additional data are needed to determine if noise exposure can enhance age-related changes in VOR cancellation.

Disclosures: A. Velisar: None. A. Visht: None. N.M. Shanidze: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.08/Web Only

Topic: E.05. Auditory and Vestibular Systems

Support: RS-2022-NR073383
RS-2023-00210073

Title: Which factors influence the deterioration in vestibular function?

Authors: J. LEE¹, *H. LEE²;

¹Dept. of Otorhinolaryngology, Ilsan Paik Hospital, Inje Univ. Col. of Medicine, Goyang, Korea, Goyang, Korea, Republic of; ²Dept of Otolaryngology, Incheon St. Mary's Hospital, The Catholic Univ. of Korea., Incheon, Korea, Republic of

Abstract: Objectives: We aimed to investigate the prevalence and age-related changes in vestibular function within the general population using survey data from the Korean National Health and Nutrition Examination Survey (KNHANES) and examine the potential factors influencing it. **Methods:** We analyzed retrospective data from 1,270 participants from the 2021 KNHANES who completed both the video head impulse test and audiometric evaluations. Participants with vestibulo-ocular reflex (VOR) gains < 0.8 and > 1.2 were excluded to minimize the impact of possible testing errors and prior impaired vestibular function. We assessed the prevalence and age-related changes in vestibular function and analyzed potential influencing factors using logistic regression analysis. **Results:** The VOR gain decreased with age; however, statistical significance was not achieved (coefficient -0.0003, $p = 0.281$). The presence of corrective saccades significantly increased with age ($p < 0.001$), with those in their 70s being 3.98 times more likely to exhibit corrective saccades than those in their 40s. The overall prevalence was 17.08%. Subjects with corrective saccades exhibit lower VOR gain than those without it ($p < 0.001$). Age, sex, hypertriglyceridemia, and hearing levels at 4,000 Hz were significantly associated with the presence of corrective saccades. **Conclusion:** Vestibular function declined with age, influenced significantly by sex, hypertriglyceridemia, and hearing level at 4,000 Hz. The increased prevalence of corrective saccades among older adults underscores the importance of early detection and intervention. Understanding age-related changes in vestibular function can facilitate appropriate management strategies and countermeasures at the personal and societal healthcare level.

Disclosures: J. Lee: None. H. Lee: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.09/J9

Topic: E.05. Auditory and Vestibular Systems

Title: Bridging the Gap Between Motor & Non-Motor Symptoms in Parkinson's Disease using Vestibular Measures

Authors: *C. ALVAREZ¹, A. DANESH²;

¹Florida Atlantic Univ., Boca, FL; ²Communication Sci. and Disorders, Florida Atlantic Univ., Boca Raton, FL

Abstract: Parkinson's Disease (PD) has historically been regarded as a neurodegenerative motor disorder due to both the clinical presentation of motor deficits and robust nigrostriatal dopaminergic degeneration. However, with increasing evidence of multi-system neurodegeneration, combined with growing reports of heterogeneous manifestations of non-motor symptoms, this view has shifted. These developments in our knowledge of PD have expanded the clinical approach for diagnosis and treatment interventions to better understand the relationship between motor and non-motor symptoms. Among these findings emerged pathological evidence of degeneration to the neural circuitry of the vestibular system, a critical system responsible for maintaining balance, spatial awareness, and modulating cognition, highlighting a potential shared mechanism to understand motor and non-motor symptoms in PD. While there is evidence for vestibular dysfunction in PD, this field remains largely under-investigated and poorly understood, particularly regarding its relation to motor and non-motor symptoms. In addition to pathological evidence, clinical reports of peripheral vestibular system dysfunction have been found to correlate with postural instability and gait disturbance (PIGD), a leading motor symptom of PD. Additionally, correlations between the severity of cognitive impairment and PIGD have been reported in PD, further contributing to a shared underlying mechanism between the two. These findings underscore the need to further investigate the vestibular system and its relationship with motor and non-motor symptoms in PD. This study will use innovative technology to assess multiple domains implicating central vestibular pathways, including: vestibular-spinal reflex (VSR), vestibular-ocular reflex (VOR), and vestibular domains of cognitive function. AI technology will provide quantitative data to assess VSR and motor function during gait and balance testing. Using eye-tracking technology, quantitative measures will be used to assess VOR and innovative vestibular cognitive testing. Finally, data to assess cognitive function will be obtained using a novel electronic cognitive screening tool, in addition to traditional testing using the Montreal Cognitive Assessment. Altogether, this study will investigate how the interplay between motor, cognitive, and vestibular function affects patients with PD, contributing to a more comprehensive understanding of the challenges faced by these individuals.

Disclosures: C. Alvarez: None. A. Danesh: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.10/Web Only

Topic: E.05. Auditory and Vestibular Systems

Support: 2022R1F1A1071824
RS-2023-00210073

Title: Brain metabolism in Vestibular Neuritis - Preliminary study using fNIRS

Authors: H. LEE¹, *J. LEE²;

¹Dept of Otolaryngology, Incheon St. Mary's Hospital, The Catholic Univ. of Korea., Incheon, Korea, Republic of; ²Ilsan Paik Hospital, Inje Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Objective: fNIRS (functional near-infrared spectroscopy) is an optical brain monitoring technique which uses near-infrared spectroscopy for the purpose of functional neuroimaging. The aim of the study is to investigate the brain metabolism in the patients with acute vestibular neuritis during vestibular stimulation using fNIRS. Methods: Four patients with acute vestibular neuritis were enrolled in the study. Brain metabolisms were measured using fNIRS while the patients were in resting states and in vestibular stimulated states (6th position in posturogram), and compared. Also, they were compared with those of normal healthy subjects. Results: When the subjects were stimulated, brain metabolisms in the visual cortex, superior temporal gyrus, and pre/ postcentral gyrus, which are known to be associated with a multisensory (vestibular) cortical circuit, showed meaningful changes. Among them. VN patients and the normal healthy subjects showed opposite changes of brain metabolisms in visual cortex and pre/postcentral gyrus. Conclusion: A multisensory cortical network is associated during vestibular stimulation, and their activation/deactivation are different in VN patients and the normal healthy subjects. fNIRS can provide precious information on brain metabolism regarding dizzy patients.

Disclosures: H. Lee: None. J. Lee: None.

Poster

PSTR024: Vestibular Processing and Perception

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR024.11/J10

Topic: E.05. Auditory and Vestibular Systems

Support: This work was partially funded by a Rubenstein Foundation grant (MCS and KEC) and by the Lloyd B. Minor Center for Vestibular and Skull Base Sciences (JPC).
KEC was supported by the following NIH Grants: R01-DC002390, R01-DC018061, and 1UF1NS111695-01.
MCS was supported by the following DoD Grants: W81XWH-15-1-0442, and W81XWH-17-CTRR-CTA.
RA was supported by the T32 Postdoctoral Training Grant

Title: Impacts of unilateral superior canal dehiscence syndrome on balance kinematics

Authors: *R. ARYAN¹, J. L. MILLAR², J. P. CAREY³, M. C. SCHUBERT³, K. E. CULLEN⁴; ¹Biomed. Engin., ²Physical Med. and Rehabil., ³Otolaryngology-Head and Neck Surgery, Sch. of Medicine, The Johns Hopkins Univ., Baltimore, MD; ⁴Dept. of Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: Superior canal dehiscence (SCD) is a pathological opening in the bone overlying the superior semicircular canal, forming a third mobile window that corrupts pressure and sound transmission in the ear. This leads to sound or pressure-induced stimulation of the canal. Affected individuals report various auditory and vestibular symptoms (SCD syndrome; SCDS) including chronic imbalance. However, balance kinematics in this population have not been objectively characterized. The present study investigated whether the kinematics of balance control are altered in unilateral SCDS. We hypothesized that kinematics about the pitch axis would be most altered given that the superior canal orientation is sensitive to pitch.

Methods: Sixteen individuals with unilateral SCDS and 16 healthy controls were included (mean age 47 years). Two inertial measurement units (IMU) were placed on the back of the head and the waist (nearly at the level of center of mass) to capture 3D angular and linear kinematics during six 30s balance tasks under different proprioceptive and vestibular conditions (vision: eyes open/closed; base of support: firm/foam/tandem). Task duration, range and standard deviation (SD) of kinematic measures, along with balance and symptom severity questionnaires and vestibular physiological tests were compared between groups.

Results: Controls maintained a longer tandem stance with eyes closed ($p < 0.001$). Compared to controls, SCDS group showed significantly greater waist kinematics not only along the pitch but also across the other axes. In the SCDS group, waist roll, pitch, and yaw velocity ranges—as well as lateral, vertical, and anteroposterior accelerations—were significantly greater in most tasks ($p < 0.05$). Variability (SD) of all waist velocities and lateral acceleration were elevated in all 6 tasks ($p < 0.05$). Head IMU data showed increased roll and pitch velocity ranges in 4 of 6 tasks, except for roll velocity during firm surface stance with eyes open and tandem stance with eyes closed, and pitch velocity during firm surface stance with eyes open and closed. SD of head roll and pitch velocities was greater in 5 of 6 tasks ($p < 0.05$) except during firm surface stance with eyes open. Furthermore, range of head kinematics in SCDS significantly correlated with perceived dizziness and oscillopsia.

Conclusion: Individuals with SCDS exhibit altered balance and head stability across multiple axes, particularly roll and pitch. The increased kinematic ranges in unilateral SCDS patients suggest reduced postural and head stability, especially without vision or with narrow or unstable base of support.

Disclosures: R. Aryan: None. J.L. Millar: None. J.P. Carey: None. M.C. Schubert: None. K.E. Cullen: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.01/J11

Topic: E.06. Vision

Support: NEI EY01844
EY27193
EY36811

Title: Photoreceptor degeneration induces homeostatic rewiring of rod bipolar cells

Authors: *P. BONEZZI, R. FREDERIKSEN, K. KIM, A. TRAN, G. L. FAIN, A. P. SAMPATH;
Ophthalmology, Jules Stein Eye Inst., Los Angeles, CA

Abstract: Retinal degeneration is known to trigger rewiring of retinal circuitry, which has often been considered maladaptive for vision. We have previously shown, however, that cones lacking outer segments and synaptic pedicles continue to display light responses with reduced sensitivity, which are passed to second-order bipolar cells. Retinal ganglion cells retain a surprising level of sensitivity despite the more profound loss of outer retinal signals. Here, we test the hypothesis that rod bipolar cells (RBCs) re-wire with cones to form functional synapses, which communicate significant visual information to the inner retina during degeneration. We used whole-cell patch-clamp to record light-evoked responses of RBCs and cone bipolar cells (CBCs) in four mouse models: *Gnat1*^{-/-}, lacking the rod-specific G protein transducin; *Elfn1*^{-/-}, lacking the extracellular adhesion protein required for synapse formation between rods and RBCs; *Rho*^{-/-}, a model of slow degeneration lacking rhodopsin; and *P23H*^{+/-}, another model of slow rod degeneration caused by misfolded rhodopsin. Recording pipettes contained fluorescent dye to permit imaging and subsequent identification of bipolar cell subtypes. We found that in degenerated retinas (*Rho*^{-/-}), RBCs exhibited robust responses ($-20 \text{ pA} \pm 10 \text{ pA}$; $n = 30$) with responses in a majority of the cells exceeding 10 pA. Comparatively, both *Gnat1*^{-/-} ($-4 \pm 1 \text{ pA}$; $n = 23$) and *Elfn1*^{-/-} ($-3 \pm 1 \text{ pA}$; $n = 16$) RBCs were mostly silent, while occasionally exhibiting small light responses. Preliminary findings in *P23H*^{+/-} retinas show that RBCs are driven by both rod and cone inputs, which vary depending on the stage of photoreceptor degeneration. In all other models, RBCs were highly desensitized, responding only at cone light levels. Imaging RBCs after each recording revealed cell bodies located distally and long axons terminating proximally in sublamina b of the IPL. For each RBC, we also confirmed the viability of each retinal slice by recording from and imaging an adjacent CBC. The presence of significant light-evoked RBC responses at cone intensities in *Rho*^{-/-} mice reveals that RBCs must rewire to cone photoreceptors during the degenerative process. Such large RBC responses are not observed when rod light responses are eliminated (*Gnat1*^{-/-}) or when rod-to-RBC synapses do not form (*Elfn1*^{-/-}). We suggest that additional stressors resulting from photoreceptor degeneration, independent of light-evoked responses or synapse formation, may promote RBC rewiring to protect visual sensitivity.

Disclosures: P. Bonezzi: None. R. Frederiksen: None. K. Kim: None. A. Tran: None. G.L. Fain: None. A.P. Sampath: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.02/J12

Topic: E.06. Vision

Support: NIH Grant R00EY031333

Title: Photoswitch DENAQ restores wild-type level retinal acuity in the blind retina

Authors: *J. JIN, D. BABINO;

Neurosci. and Ophthalmology, SUNY Upstate Med. Univ., Syracuse, NY

Abstract: Restoring vision in patients with retinal degeneration remains a critical unmet need. Photoswitches, light-sensitive small molecules, offer a non-genetic strategy to restore light sensitivity to retinal ganglion cells (RGCs) by modulating ion channel activity. BENAQ, an azobenzene based photoswitch, has restored light responses in blind rd1 mouse retinas and progressed to Phase II clinical trials. Building on this progress, we investigated DENAQ, a related compound with enhanced properties, using EyeCandy, our ex vivo multielectrode array platform for quantifying retinal acuity. We projected both static (grating contrast) and dynamic (speed varying) stimuli onto treated retinas while recording RGC activity. Wild type retinas exhibited approximately 0.4 cycles per degree (cpd) acuity, while untreated rd1 retinas showed none. DENAQ treated retinas demonstrated improved outcomes across three key metrics: (1) broader retinal delivery and activation; (2) restoration of both binary type responses; and (3) significantly higher acuity (0.15 cpd versus 0.07 cpd with BENAQ). Unlike BENAQ, DENAQ treated retinas also responded to dynamic stimuli with speed sensitivity resembling wild type retinas. These findings highlight DENAQ as a promising photoswitch that restores both light sensitivity and essential functional features of vision.

Disclosures: J. Jin: None. D. Babino: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.03/J13

Topic: E.06. Vision

Support: Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2024-00407321)

Title: Ectopic synaptogenesis during retinal degeneration in mice after blue-LED injury

Authors: *D. KIM¹, Y. HEO¹, K.-W. SUNG², Y. PARK¹;

¹Anat., Col. of Medicine, The Catholic Univ. of Korea, Seoul, Korea, Republic of; ²Pharmacol., College, of Medicine, The Catholic Univ. of Korea, Seoul, Korea, Republic of

Abstract: Objective: Retinal degeneration (RD), a major cause of blindness worldwide, usually involves photoreceptor death resulting in sensory deafferentation of the inner retina. To compensate for this discontinuity in the visual signaling cascade, synaptic remodeling of the retina occurs. In this study, we aimed to investigate the morphological development of ectopic synapses, evaluate retinal function over time after initiation of RD, and identify key genes involved in the synaptic remodeling process. Methods: BALB/c mice were exposed to blue LED (460 nm) for 2 hours to induce RD. The timepoints for investigation were 72 hours, 1 month, 2 months, and 3 months after exposure. The state of synaptogenesis was assessed by immunohistochemistry (IHC) with anti-protein kinase C alpha (PKC α), anti-vesicular glutamate transporter 1 (VGLUT1), and anti-calbindin. The structural morphology was further examined using electron microscopy (EM). Next, retinal function was evaluated using scotopic electroretinography (ERG). Finally, RT-qPCR was conducted for various synaptogenesis-related genes. Results: IHC analysis showed the number of triple-stained dendrites increased as duration after exposure increased, with the difference between groups being statistically significant except for 1 month vs. 2 months and 2 months vs. 3 months. At 1 month, EM examination revealed immature ribbon synapses with free photoreceptor axon terminals. By 3 months, mature ectopic synapses with proper bipolar and horizontal cell dendrite invaginations were observed. In ERG analysis, the a wave absolute amplitude was statistically significantly lower at 2 and 3 months vs. Normal, but there was no difference in b wave amplitudes. In addition, the absolute b/a ratio was higher at 3 months vs. 1 month. Finally, brain-derived neurotrophic factor (BDNF) and growth associated protein 43 (GAP43) expression increased starting at 1 month and remained at about 2 x fold, compared to that of normal mice retinæ, until 3 months. Conclusion: In response to deafferentation during RD, rod bipolar cells undergo structural remodeling and form functional ectopic synapses in the EM level. BDNF and Gap43 are key genes in this process, and thus warrant further investigation into their pathophysiological role and therapeutic potential during RD.

Disclosures: D. Kim: None. Y. Heo: None. K. Sung: None. Y. Park: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.04/J14

Topic: E.06. Vision

Support: NIH Grant RO1EY028039
NIH Grant R01NS114397

Title: Recovery of retinal terminal fields after traumatic brain injury: evidence of collateral sprouting and sexual dimorphism

Authors: *A. S. ALEXANDRIS¹, J. YI², C. LIU², J. BELAMARICH², Z. ALAM², A. PENG², D. S. WELSBIE³, D. J. ZACK², V. E. KOLIATSOS²;

¹Pathology, ²Johns Hopkins Univ., Baltimore, MD; ³Ophthalmology, UCSD, La Jolla, CA

Abstract: The central nervous system (CNS) exhibits limited regenerative capacity, yet examples of functional recovery after injury suggest a remarkable potential for repair. Traumatic brain injury (TBI) disrupts connectivity through traumatic axonal injury (TAI), the most common neuropathology in TBI, yet the mechanisms enabling circuit restoration after diffuse injury remain poorly understood. Most previous studies have focused on focal or complete injuries, where robust sprouting often involves heterotypic or maladaptive pathways, limiting translational relevance. Here, we investigate homotypic collateral sprouting—compensatory branching of surviving axons within their native target field—in the context of diffuse TAI, using a mouse impact-acceleration TBI model that better reflects human pathology. Retinal ganglion cell (RGC) axons and synapses were genetically labeled via intravitreal AAV transduction, with anterograde and transsynaptic tracers to map terminals and postsynaptic partners. Functional connectivity was assessed using postsynaptic c-Fos expression following light stimulation and visual evoked potentials (VEPs). Our data reveal that TAI induces an initial ~50% loss of RGC axons and retinocollicular terminals, with corresponding deficits in postsynaptic activation and pattern VEPs. Remarkably, surviving RGCs undergo rapid homotypic collateral sprouting, restoring terminal density and function to near baseline within 14 days post-injury, demonstrating robust structural and functional repair in a diffuse injury context. Notably, female mice show delayed or incomplete recovery, indicating sex-specific constraints on CNS plasticity. Furthermore, Sarm1 deletion blocks Wallerian degeneration but does not prevent terminal restoration, highlighting mechanistic independence between these processes. These findings identify homotypic collateral sprouting as a key driver of circuit repair after diffuse TAI, distinguishing it from earlier models of focal injury and offering insights into therapeutic strategies that consider sex differences in CNS plasticity.

Disclosures: A.S. Alexandris: None. J. Yi: None. C. Liu: None. J. Belamarich: None. Z. Alam: None. A. Peng: None. D.S. Welsbie: None. D.J. Zack: None. V.E. Koliatsos: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.05/J15

Topic: E.06. Vision

Support: EY035885

Title: Increased neuronal plasticity Accelerates Vision Deficits in the P23H murine model of Retinitis Pigmentosa

Authors: *T. C. BROWN;
Univ. of Arizona Col. of Med., Phoenix, AZ

Abstract: Retinitis pigmentosa (RP) is a neurodegenerative condition of blindness affecting over one hundred thousand Americans and over a million people worldwide. RP is characterized by progressive loss of rod photoreceptors followed by cone photoreceptors that manifests in progressive loss of vision. Clinical diagnosis is often at advanced disease stages of the disorder and there are no available therapeutic interventions at present. The P23H rhodopsin mutation is an autosomal-dominant form of RP. Mice heterozygous for this mutation (rho P23H/+) display degeneration of photoreceptors and reduced amplitudes for the electroretinogram. Here we set out to quantify loss of visual function in the mouse model of RP then test if increasing neuronal plasticity throughout the brain by genetically ablating nogo receptor (ngr1 -/-), a known method of increasing cortical plasticity and rescuing other visual disorders, would attenuate disease progression. First, we assessed visual acuity using the visual water task (VWT) under light-adapted conditions (100 cd/m²) and dark-adapted conditions (.02 cd/m²). P23H mice displayed progressive losses of visual acuity under both conditions with deficits in dark-adapted conditions preceding those in light-adapted conditions. Second, we assessed functional tuning properties of excitatory neurons in primary visual cortex (V1) under light-adapted conditions and dark-adapted conditions utilizing in vivo 2-photon microscopy in awake mice. Tuning properties of neurons were affected by age and light conditions. P23H mice had significantly fewer responding neurons to higher spatial frequencies under both conditions. Additionally, visual acuity assessed by the VWT could be predicted from spatial frequency tuning response curves. Finally, we examined mice with mice in this same experimental paradigm. Surprisingly, rho P23H/+; ngr1 -/- exhibit greater deficits in visual acuity and neuronal response properties when compared to both control and P23H mice. Here we determined that rho P23H/+ mice have progressive loss of visual function. We also have determined that behavioral visual acuity can be inferred from the receptive field tuning properties of neurons in V1. This provides a basis in neuronal function for loss of vision. Finally, and contrary to our hypothesis, we determined that increasing neuronal plasticity accelerates loss of both visually driven behavior and neuronal response properties in cortex. This research provides a foundation for increasing plasticity in the brain could have marked deleterious effects in neurodegenerative conditions.

Disclosures: T.C. Brown: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.06/J16

Topic: E.06. Vision

Title: Visual cortex activation accelerated the synapse plasticity in LGN and improved vision loss in retina ischemic mouse model

Authors: *X. JIA¹, Y. J. LIAO²;

¹Stanford Univ., Stanford, CA; ²Stanford Univ., Palo Alto, CA

Abstract: **Title:** Visual cortex activation accelerated the synapse plasticity in LGN and improved vision loss in retina ischemic mouse model. **Purpose:** Optic neuropathies such as non-arteritic anterior ischemic optic neuropathy (AION) result in irreversible vision loss due to retinal ganglion cell degeneration and optic nerve damage. While current treatment options are limited, eye and brain electrical stimulation may offer a therapeutic entry point. This study explores the effective of activation of eye and the primary visual cortex (V1) on AION mouse model. **Methods:** We employed a chemogenetic approach, in which an excitatory DREADD receptor (hM3Dq) derived by the CaMKII promoter is delivered into the eye or V1 area of mice conveyed by AAV9 vector. Following viral expression, unilateral AION was induced via laser photothrombosis method. Four days post-AION, mice received daily CNO or saline injections to activate eye or V1 excitatory neurons over a two-week period. Retina structure and visual function were assessed using optical coherence tomography (OCT) and optokinetic response (OKR). To evaluate visual neural circuitry connection, we performed protein omic and immunostaining for synaptic structure analysis in the LGN at 25 days post-AION. **Results:** We evaluated the visual circuit following AION induction and found the retinageneculate connection disrupted in IHC and TEM experiments. Chemogenetic activation of V1 neurons led to notable neuroprotective and visual functional benefits. In detail, Mice receiving CNO treatment exhibited preserved retinal thickness in the injured eye and significant recovery in visual behavior compared with saline injection group, while eye stimulation has no such effective. Importantly, our protein omic and IHC experiments show the synaptic remodeling in the contralateral LGN following V1 stimulation, suggesting enhanced synapse plasticity. **Conclusion and significance:** Our findings demonstrate that the visual cortex stimulation can repair the injured visual system. Activating V1: CaMKII neurons not only restores retinal structure and visual behavior but also promotes synaptic plasticity in the thalamus. This strategy represents a novel therapeutic avenue for AION and potentially other forms of optic neuropathy.

Disclosures: X. Jia: None. Y.J. Liao: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.07/K1

Topic: E.06. Vision

Support: CIHR – PST [178259]
CIHR - PST [190077]
NSERC – RGPIN – [2022-05068]

Title: Morphological modification of y cells in the lateral geniculate nucleus following perinatal auditory deprivation

Authors: *N. D. MURPHY^{1,2}, S. G. LOMBER^{1,2};
¹Physiol., McGill Univ., Montreal, QC, Canada; ²Psychology, Univ. of Texas at Arlington, Arlington, TX

Abstract: The brain exhibits a remarkable ability to reorganize following abnormal sensory experience. It remains unclear how intact visual areas may be modified to compensate for the loss of auditory input following auditory deprivation. Specifically, it is unknown how the lateral geniculate nucleus (LGN) develops in the absence of competing auditory input. In the absence of auditory input, exuberant projections to the LGN which are typically pruned across development are thought to be preserved to allow for enhanced visual processing. Y cells in the LGN relay motion information and are a promising substrate for investigating compensatory plasticity in the thalamus. Immunohistochemical labelling of Y cells was performed using SMI-32, an antibody targeting the heavy chain of non-phosphorylated neurofilament protein. Unbiased systematic random sampling was employed to quantify Y cell morphology in the LGN of hearing (N = 2 hemispheres) and perinatally ototoxically deafened (N = 2 hemispheres) cats (F = 1, M = 1). Branched structure analysis was performed using Neurolucida Explorer (Williston, VT, USA) to assess LGN layer surface area, soma volume, dendrite number, length and branch order. Differences between hearing and deaf subjects were assessed using Mann-Whitney U tests. Within conditions, differences across layers were assessed using Kruskal-Wallis tests. No differences in soma volume were appreciated in any layer however, C-Complex soma volume was significantly lower than those in layers A and A1 ($p < 0.001$). The number of dendrites in layers A and C-Complex between hearing and deaf subjects was equal, but deaf subjects revealed fewer dendrites in layer A1 compared to hearing ($p = 0.0026$). In both conditions, neurons in layers A and A1 had a significant increase in the number dendrites per neuron compared to the C-Complex ($p < 0.0001$). Dendrites were significantly longer in deaf subjects in layer A ($p = 0.0031$) and layer A1 ($p = 0.00043$), but not in the C-Complex. In all cases, dendrites were longer in layers A and A1 compared to the C-Complex ($p < 0.001$). Deaf subjects revealed an increase in higher-order branches in layers A and A1 ($p < 0.0001$), but not in the C-Complex. In both conditions, neurons were more branched in layers A and A1 compared to C-Complex ($p < 0.001$). Overall, Y cells in layers A and A1 of deaf subjects were significantly longer and more branched compared to those in hearing subjects. No morphological differences were observed in the C-Complex. These preliminary data suggest that small-scale morphological changes occur in the early visual system as a consequence of auditory deprivation. Data collection continues for 8 subjects.

Disclosures: N.D. Murphy: None. S.G. Lomber: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.08/K2

Topic: E.06. Vision

Support: R01AG064067

Title: Excitatory and inhibitory synaptic traces of visual recognition memory

Authors: *J. DODERER¹, J. SUBRAMANIAN²;

²Dept. of Pharmacol. and Toxicology, ¹Univ. of Kansas, Lawrence, KS

Abstract: Repeated exposure to a visual stimulus leads to suppressed neural responsiveness to the familiar stimulus and enhanced responsiveness to unexpected deviations. However, the synaptic mechanisms underlying this adaptive plasticity remain incompletely understood. Here, we characterize the structural adaptations of excitatory and inhibitory synapses associated with repeated exposure to orientation grating stimuli and assess how these processes are disrupted in a mouse model of Alzheimer's disease (AD). Using multicolor two-photon in vivo synaptic imaging, we show that repeated passive visual experience modulates both the dynamics and spatial clustering of excitatory and inhibitory synapses. These experience-dependent synaptic adaptations are impaired in the presence of AD pathology. Finally, we test whether locally clustered dynamics of excitatory and inhibitory synapses contribute to the suppression of responses to familiar stimuli and the enhancement of responses to deviant stimuli.

Disclosures: J. Doderer: None. J. Subramanian: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.09/K3

Topic: E.06. Vision

Support: NIH Grant R01-MH122478 (to AAB, AH, and MS)
NIH Grants F32-EY029935, K99-EY033976 (to BR)
NIH Grant R01-EY02874 (to MS)

Title: Transcriptional Signatures of Visual Cortex Plasticity During Endogenous and Transplant-Induced Critical Periods

Authors: *P. MARCHETTA¹, N. SANTIAGO², B. RAKELA³, D. STEFFEN⁴, A. ALVAREZ-BUYLLA⁵, M. P. STRYKER³, A. R. HASENSTAUB²;

¹Dept. of Otolaryngology-Head and Neck Surgery,, ²Dept. of Otolaryngology-Head and Neck

Surgery, ³Dept. of Physiol. and Ctr. for Integrative Neurosci., ⁴Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., Univ. of California, San Francisco, San Francisco, CA; ⁵Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., Univ. of California San Francisco, San Francisco, CA

Abstract: Transplantation of embryonic cortical interneuron (cIN) precursors from the medial ganglionic eminence (MGE) into postnatal visual cortex induces a second period of activity-dependent plasticity. This plasticity resembles the normal juvenile critical period (CP) of susceptibility to the effects of monocular visual deprivation (MD). The endogenous, juvenile CP lasts about one week, around 35 days after the birth of parvalbumin- and somatostatin-expressing cINs. The transplant-induced CP also occurs 35 days after transplantation, when the host is much older. While CP plasticity has been studied extensively at circuit and cellular levels, the underlying genes that coordinate its initiation, maintenance, and closure remain poorly understood. Identifying these genes is essential for uncovering the molecular basis of sensory plasticity and could inform therapeutic strategies for neurodevelopmental disorders. To investigate these mechanisms, we compared the endogenous and transplant-induced CPs by single-cell RNA sequencing (scRNA-seq) of mouse visual cortex at three time points (“pre” before MD, 1 day after MD at the peak of the CP, and “post” 9 days after the 5-day MD). Both control intact and MD animals were included, and the effect of transplantation was controlled using sham surgery. MGE tissue was dissected from Nkx2.1;Ai14 donor mice and transplanted into adult mice, allowing confirmation of the presence of transplanted cells in the host visual cortex. Transplanted and sham-injected animals were sampled at matched time points with 2 biological replicate pools at each. This experimental design enables comparison of gene expression dynamics between endogenous and transplant-induced CPs at single-cell resolution. By analyzing gene expression across diverse cortical cell types in both contexts, we aimed to identify shared and distinct molecular programs governing cortical plasticity. The most striking findings to date are from a cluster analysis of the expression of the 1000 genes that differed the most between MD and control during the endogenous CP. MD changed the expression of several clusters (comprising about half of the 1000 genes) similarly during the endogenous and transplant-induced CPs, but only for the transplanted mice and not for the shams. Both increases and decreases were seen in different neuronal cell types, and MD also produced changes in non-neuronal cell types. These insights may begin to reveal mechanisms by which plasticity can be re-engaged in the mature brain and support future strategies for neural repair or rehabilitation.

Disclosures: **P. Marchetta:** None. **N. Santiago:** None. **B. Rakela:** None. **D. Steffen:** None. **A. Alvarez-Buylla:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arturo Alvarez-Buylla is cofounder, serves on the scientific advisory board, and owns shares in Neurona Therapeutics.. **F. Consulting Fees** (e.g., advisory boards); Arturo Alvarez-Buylla is cofounder, serves on the scientific advisory board, and owns shares in Neurona Therapeutics.. **M.P. Stryker:** None. **A.R. Hasenstaub:** None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.10/K4

Topic: E.06. Vision

Support: NIH K99-EY033976
NIH K99-EY029002
NIH R01-EY02874
MEC GR001264

Title: Gabaergic signaling by vip interneurons gates state-dependent visual recovery in adult cortex

Authors: A. LEBEDEVA¹, F. KLING², B. RAKELA³, M. P. STRYKER⁴, *Y. SUN²;
¹Sainsbury Wellcome Ctr., ²Univ. Col. London, London, United Kingdom; ³Neurosci., ⁴Ctr. for Integrative Neurosci, Dept Physiol, Univ. of California San Francisco, San Francisco, CA

Abstract: Running enhances responses and plasticity in the visual cortex of adult mice, a process previously shown to require vasoactive intestinal peptide (VIP)-expressing interneurons. VIP cells signal via both GABA and the VIP neuropeptide, and the distinct roles of these outputs in adult cortical plasticity remain unknown. Here, we use longitudinal two-photon calcium imaging in awake, behaving adult mice to dissect the contributions of GABAergic versus peptidergic signaling from VIP interneurons during monocular visual deprivation (MD) and subsequent recovery. We disrupted either GABA release (VIP-Cre;Vgat^{fl/fl}) or VIP production (VIP^{-/-}) genetically and monitored ocular dominance plasticity and binocular recovery in layer 2/3 neurons of V1. Both groups exhibited robust ocular dominance shifts after MD, indicating that neither output from VIP cells is required for the initial deprivation-induced plasticity. However, functional recovery of deprived-eye responses during binocular visual experience was selectively impaired in mice with impaired GABA release from VIP cells. This deficit was evident when measured under both running and still conditions. Moreover, we showed that locomotion preferentially enhanced visual responses to the contralateral eye, and this eye-specific bias was altered during binocular recovery. Control animals showed a normalization of this modulation after recovery, while GABA-deficient mice displayed an aberrant shift favoring the ipsilateral eye. GABAergic signaling by VIP interneurons is thus essential for behaviorally driven sensory restoration. These findings reveal a novel circuit mechanism linking behavioral state to adult cortical plasticity and highlights VIP cell-mediated inhibition as a potential target for restoring sensory function. We thank Prof. J.A. Waschek of UCLA for the gift of VIP-knockout (VIP^{-/-}) mice.

Disclosures: A. Lebedeva: None. F. Kling: None. B. Rakela: None. M.P. Stryker: None. Y. Sun: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.11/K5

Topic: E.06. Vision

Support: NIH Grant EY034092

Title: Degraded mapping of disparity tuning in visual cortex explains deficits in binocular depth perception

Authors: T. C. BROWN¹, C. M. BARR³, A. W. MCGEE², *J. M. SAMONDS⁴;

¹ASNB, Univ. of Arizona Col. of Med., Phoenix, AR; ²Univ. of Arizona Col. of Med., Phoenix, AZ; ³Univ. of Texas at Austin, Austin, TX; ⁴Univ. of Texas At Austin, Austin, TX

Abstract: Sensory cortex is highly organized, but understanding why remains elusive. Here we demonstrate that depriving juvenile mice of vision in one eye (monocular deprivation, MD) for 30 days during the critical period for the development of binocularity caused enduring deficits in binocular depth perception. Mice with 30 days of MD mice performed significantly worse than non-deprived mice during the pole descent cliff task even after MD mice recovered with 6 weeks of normal binocular vision (N = 46 non-deprived mice, N = 51 30-day MD mice). Based on responses measured with two-photon microscopy, we found that deprivation of binocular vision severely degraded retinotopic mapping of binocular disparity tuning in the visual cortex, despite no detectable differences in the range or selectivity of disparity tuning by populations of neurons (N = 8 non-deprived mice, n = 3571 neurons; N = 12 30-day MD mice, n = 3106 neurons). Disparity tuning was strongest in the central portion of the visual field and transitioned from representing nearer to farther depths from the lower to upper visual field, respectively. This organization of disparity tuning prioritizes naturally encountered depths. Monocular deprivation caused greater uniformity in disparity across visual space and an overall shift to nearer disparities in the secondary visual area, lateromedial visual cortex (LM). Additionally, disparity tuning improved from the primary visual cortex (V1) to LM in non-deprived mice, but became worse in 30-day MD mice. Trial-to-trial variability was also significantly worse in 30-day MD mice compared to non-deprived mice. By measuring discriminability based on the responses of neurons, we demonstrate that the combination of disorganized mapping and the more unreliable trial-to-trial representation of disparity in monocular deprived mice is sufficient to explain their impaired binocular depth perception.

Disclosures: T.C. Brown: None. C.M. Barr: None. A.W. McGee: None. J.M. Samonds: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.12/K6

Topic: E.06. Vision

Support: R01-EY014882

Title: Rapid neuronal-type specific network plasticity following adult-onset blindness

Authors: ***L. MESIK**^{1,2}, **H. PHAM**^{3,2}, **A. DRAGOMIR**⁵, **N. V. THAKOR**⁶, **H.-K. LEE**^{3,2,4};
²Zanvyl-Krieger Mind/Brain Inst., ³Neurosci., ⁴Kavli Neurosci. Discovery Inst., ¹Johns Hopkins Univ., Baltimore, MD; ⁵Natl. Univ. of Singapore, Singapore, Singapore; ⁶Biomed. Engin. Dept., Johns Hopkins Med. Institutions, Baltimore, MD

Abstract: Loss of vision can result in a number of long-term morphological and functional changes in the visual cortex. However, not much is known about the evolution of cell-type specific activity and network dynamics leading up to these adaptations. We set out to explore changes in cortical dynamics within pyramidal (PYR) and inhibitory (PV, VIP, SOM) neuronal populations during the first week following enucleation. Using two-photon calcium imaging in the layer 2/3 of the mouse visual cortex, we longitudinally tracked spontaneous activity in the darkness and then 1, 3, and 7 days post-enucleation. To our surprise, the most prominent changes did not happen gradually, but instead had a sudden onset within 1 day of enucleation. These include an increase in spontaneous activity and pairwise correlations within PYR and PV subpopulations, as well as the emergence of slow oscillatory activity in the neuropil of these populations. VIP neurons also showed a slight increase in activity, albeit more delayed compared to PYR and PV. Activity of both PYR and PV became generally suppressed by whisking while VIP neurons became less positively correlated with it. Graph-theoretic analyses additionally showed rapid significant changes in the network structure of the PYR and VIP subpopulations. Together, these results indicate that loss of vision in the form of enucleation results in rapid changes within the PYR and PV populations, most prominently manifested by increased synchrony accompanied by slow network oscillations, and an increased suppressive influence of whisker-related inputs.

Disclosures: **L. Mesik:** None. **H. Pham:** None. **A. Dragomir:** None. **N.V. Thakor:** None. **H. Lee:** None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.13/K7

Topic: E.06. Vision

Support: NIH Grant R01-EY014882 to H.-K.L.

Title: Compensatory Plasticity in the Mouse Primary Visual Cortex Following Adult-onset Hearing Loss

Authors: *H. T. PHAM¹, L. MESIK², H.-K. LEE¹;
¹Neurosci., ²Johns Hopkins Univ., Baltimore, MD

Abstract: A fundamental feature of the brain is its ability to undergo structural and functional changes throughout life, optimizing our capacity to interact with the environment. This cognitive flexibility is exemplified in the nervous systems of animals deprived of a sensory modality. For instance, deafened humans have been shown to outperform hearing controls in detecting visual targets, and congenitally deaf cats exhibit enhanced peripheral vision compared to their hearing counterparts. These enhancements have been attributed to compensatory cross-modal plasticity, a phenomenon in which the spared sensory cortices undergo synaptic modifications to improve sensory processing. Supporting this, ex vivo recordings from the primary visual cortex (V1) of deafened mice have revealed potentiation of the feedforward sensory pathways in V1. However, it remains unclear whether these changes alter neural response properties in vivo and have a causal influence on behavior. To assess the potential effects of hearing loss on visual processing, we used intrinsic signal imaging to map V1 of mice through a cranial window implanted over the left hemisphere. We then performed 2-photon imaging of GCaMP8s signals to measure neural responses evoked by spatially-restricted horizontal sinusoidal grating stimuli, varying in spatial frequency and contrast level, in deafened mice compared to hearing controls. Preliminary data suggest that adult-onset deafness results in a statistically significant decrease in the visually evoked activity of layer 2/3 neurons located medially in V1, which processes information from the peripheral visual field. This reduction is observed in response to horizontal sinusoidal static gratings with spatial frequencies below 0.5 cycles per degree, as well as to horizontal sinusoidal drifting gratings across all tested contrast levels (4% to 85%). There was no significant change in the lateral V1, which represents the central visual field. Preliminary analysis of pupil diameter changes suggests that arousal state does not influence the recorded V1 activity in this experiment. We hypothesize that this decrease in neural activity in the medial V1 reflects a refinement of the circuitry to enhance the reliability of stimulus encoding, motivating further investigation into the effects of hearing loss on V1 function.

Disclosures: H.T. Pham: None. L. Mesik: None. H. Lee: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.14/K8

Topic: E.06. Vision

Support: NIH BRAIN Initiative Grant U19NS107464
NIMH Intramural Research Program ZIAMH0020967

Title: Pattern-specific plasticity in visual cortex is gated by acetylcholine

Authors: *P. K. LAFOSSE¹, H. N. MULHOLLAND², Z. ZHOU², M. H. HISTED²;
¹Janelia / HHMI, Ashburn, VA; ²Natl. Inst. of Mental Hlth., NIH / NIMH, Bethesda, MD

Abstract: To navigate the world, animals must readily adapt to new sensory information. In the cortex, this information is represented as dynamic patterns of activity across networks of neurons, which are refined with learning. The classic Hebbian theory of learning posits that coactivated neurons become functionally coupled via synaptic strengthening, possibly enabling network computations useful for behavior such as pattern amplification. However, recent work shows that photostimulation of neurons alone without behavioral engagement is not sufficient to induce plasticity (Akitake, Douglas et al., 2023), suggesting plasticity may require both neuronal coactivation and neuromodulatory signals. Acetylcholine (ACh), involved in arousal and attention and broadly released throughout the cortex, plays an important role in learning and may gate this form of behavior-dependent plasticity in neural circuits (Gold, 2003; Kang et al., 2014). To test this, we aimed to induce plasticity using holographic optogenetic photostimulation to drive activity in a select patterns of neurons (N=30-45 neurons) in mouse visual cortex (V1) while evoking ACh release across the cortex via electrical stimulation of the basal forebrain (BF) (e.g. Froemke et al., 2007). During induction, we repeatedly activated the full pattern of cells while simultaneously electrically stimulating the basal forebrain (N=200-250 repetitions). Using in vivo two-photon imaging to measure neural activity, we found that photostimulation of sub-patterns (N=10-15 neurons) derived from the full pattern evoked significantly increased responses in the other non-targeted sub-patterns as compared to before induction (N=6 of 10 sub-patterns across 4 animals; $p < 0.05$, Wilcoxon signed rank test). Importantly, the response of neurons in these non-targeted sub-patterns was significantly greater than control cells which never received photostimulation, indicating effects of plasticity are specific to the trained neurons only. Further, sham experiments in which animals received photostimulation in V1 but not electrical stimulation in BF failed to produce increased responses within the targeted pattern, suggesting a role for ACh in gating cortical plasticity. Our results reveal the potential mechanism by which behavioral context, via ACh release, could facilitate learning in the sensory cortex.

Disclosures: P.K. LaFosse: None. H.N. Mulholland: None. Z. Zhou: None. M.H. Histed: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.15/K9

Topic: E.06. Vision

Support: DOD Grant VR220084

Title: Functional neuronal changes in the visual pathway of adult mice associated with PNU-282987 treatment following ocular blast injury

Authors: *J. B. SPITSBERGEN¹, C. L. LINN²;
²Biol. Sci., ¹Western Michigan Univ., Kalamazoo, MI

Abstract: The objective of this research is to evaluate the structural and electrophysiological integrity of the mammalian visual pathway following ocular blast trauma and eyedrop treatment with PNU-282987. PNU-282987 is an alpha-7 nicotinic acetylcholine receptor agonist that has been shown to induce neurogenesis in both healthy and diseased adult mammalian retinas following eyedrop application. The hypothesis to be tested in this study is that daily eye drop application of PNU-282987 beginning immediately following ocular blast trauma causes cellular and functional changes in the mammalian visual system. A 35 PSI blast from a modified paintball gun was used to induce ocular blast injury in adult transgenic mice expressing TdTomato Muller glia (3-6 months old; both sexes). Animals were treated daily with a PBS eyedrop solution containing 1mM PNU-282987/1% DMSO post-blast for 4 weeks. Blast exposure at 35 PSI was shown to cause a significant loss of cells in all retinal layers, which was alleviated with 4 weeks of PNU-282987 treatment. Immunohistochemical analysis demonstrated double labeled TdTom positive photoreceptors (15.26% +/- 4.3) and TdTom positive retinal ganglion cells (8.75% +/- 1.2) were present in blast exposed mice that were treated with PNU-282987 for 4 weeks. Previous studies have confirmed that these new neurons originate from Muller glia. Labeling using NeuroVue dye indicates that axons from retinal ganglion cells derived from Muller glia extend through the optic nerve and through the optic tract into the brain. Various electrophysiological recordings, including electroretinogram (ERG), pattern ERG (pERG), and visually evoked potential (VEP) recordings, were taken from control, blast damaged, and blast damaged/PNU-282987 treated animals. ERG recordings demonstrate a significant decrease compared to controls in the amplitudes of the a-wave (50.51% +/- 8.9), b-wave (32.22% +/- 10), oscillatory potentials (OPs) 1 (35.63% +/- 10.6), 2 (30.62% +/- 5.5) and 3 (33.10% +/- 7.1), the photopic negative response (PhNR) (54.2 +/- 11.2), flicker frequency recordings from 5 (31.56% +/- 12.1), 10 (48.11% +/- 10.2) and 20 Hz (35.57% +/- 8.5), pERG waves (56.93% +/- 4.2) and VEP recordings (27.85% +/- 8.2) following blast exposure. 4 weeks of PNU-282987 treatment following blast exposure was associated with a significant recovery of amplitude compared to blast responses (up to 190%) in all aspects of the electrophysiological recordings listed above ($n=6$, $p<.05$). These are the first experiments designed to address PNU-282987 induced functional and morphological changes in the visual pathway after blast exposure and may lead to treatments for vision loss.

Disclosures: J.B. Spitsbergen: None. C.L. Linn: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.16/K10

Topic: E.06. Vision

Support: DOD Grant VR220084

Title: An alpha 7 nicotinic acetylcholine receptor agonist treatment induces retinal neurogenesis and restores electrophysiological function following blast-induced ocular trauma in adult mice

Authors: *G. V. NOLASCO DE CARVALHO¹, J. B. SPITSBERGEN², D. M. LINN, Jr.³, C. L. LINN²;

¹Biol. Sci., Western Michigan Univ., Kalamazoo, MI; ²Western Michigan Univ., Kalamazoo, MI; ³Grand Valley State Univ., Allendale, MI

Abstract: This study was designed to characterize the extent that PNU-282987, an $\alpha 7$ nAChR agonist, induces neurogenesis across all retinal layers following blast-induced ocular trauma. In addition, functional recovery was assessed using ERG recordings. Blast injuries were induced in adult mice (3-8 months, male and female) using a modified paintball gun at 35-psi. One month post blast, mice began treatment with PBS eye drops containing either 1% DMSO/1 mg/mL BrdU or 1 mM PNU-282987/BrdU. ERG recordings were conducted before blast exposure and every week following for two months with or without PNU-282987 treatment. At the end of two months, retinas were processed immunohistochemically for BrdU incorporation and for retinal cell markers. PhNR analysis revealed that PhNR amplitudes significantly decreased by an average of 50.64% $\pm$ 12.2 following blast trauma. However, after PNU-282987 treatment, amplitudes significantly increased to 143.24% $\pm$ 20.6 (N=7) when compared to control. For pERG recordings, analysis of the P1/N2 amplitudes demonstrated a significant reduction following blast injury, by 63.11% $\pm$ 6.4 (N=8) relative to controls. After blast and treatment with PNU-282987, amplitudes significantly recovered by 68.32% $\pm$ 22.6 (N=4) from blast levels. Additionally, pERG recordings revealed a progressive increase in P1 latencies following blast injury, from a mean latency of 74.25 $\pm$ 3.2 ms (N=8) under control conditions, to 98.62 $\pm$ 6.1 ms (N=7) after blast, and to 137.83 $\pm$ 4.5 ms (N=3) after blast/PNU-282987 treatment. In IHC studies, BrdU incorporation was seen throughout the neural retina after PNU-282987 treatment of blast trauma. Following blast injury, retinal cell counts in flat mounts decreased significantly by 23.2 $\pm$ 4.5 (N=6) relative to controls (N=8) within the retinal ganglion cell layer. In contrast, administration of PNU-282987 that began 1-month post-blast, significantly increased total cell counts to 115% $\pm$ 7.2 (N=6) compared to controls. 28.2% $\pm$ 3.6 of cells were BrdU positive after blast with PNU-282987 treatment, indicating neurogenic activity. In triple labeled sections for BrdU, recoverin, and DAPI, blast exposure reduced photoreceptor cell counts by 18.9 $\pm$ 2.6 (N=6) relative to controls (N=8). PNU-282987 treatment post-blast restored photoreceptor numbers to 110.2% $\pm$ 12.8 compared to control levels and demonstrated 15.8 $\pm$ 2.5 (N=6) of cells co-labeled for BrdU and recoverin. These findings demonstrate that PNU-282987 enhances retinal neurogenesis and facilitates functional recovery following blast-induced ocular trauma.

Disclosures: G.V. Nolasco de Carvalho: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.17/K11

Topic: E.06. Vision

Support: NEI EY035803

Title: Transcriptomic and immunocytochemical analysis of Müller Glia reprogramming induced by $\alpha 7$ nAChR-activated RPE signaling

Authors: *H. K. VANZO-SPARKS¹, D. M. LINN, Jr.², C. L. LINN¹;

¹Biol. Sci., Western Michigan Univ., Kalamazoo, MI; ²Biomed. Sci., Grand Valley State Univ., Allendale, MI

Abstract: Previous work from this laboratory has shown that the selective $\alpha 7$ nicotinic acetylcholine receptor (nAChR) agonist, PNU-282987, induces neurogenesis in adult murine models. These findings suggest that PNU-282987 acts on $\alpha 7$ nAChRs expressed in the retinal pigment epithelium (RPE), triggering the release of a signaling molecule that influences the apical processes of Müller glia (MG). This molecule is hypothesized to promote MG proliferation and progenitor cell formation. While the RPE response to PNU-282987 has been partially characterized, the mechanisms driving the shift in MG fate from reactive gliosis to neurogenesis remain unclear. In the present study, we investigate this process using transcriptomic profiling and immunocytochemistry (ICC). Primary MG cultures derived from adult mice were treated with conditioned media collected from primary RPE cells exposed to 100 nM PNU-282987 with 1% DMSO (experimental) or 1% DMSO alone (control) at 2, 4, 6, 8, and 12 hours. RNA-seq libraries were generated and sequenced, with read alignment to the *Mus musculus* GRCm39 reference genome and differential expression analysis performed via DESeq2. Pathway enrichment analysis identified significant activation ($\log_2FC \geq 1$ or ≤ -1 ; adjusted $p \leq 0.05$) of Wnt, BMP, and Sonic Hedgehog signaling cascades. Key components of these pathways, including *Lef1*, *Ptch1*, and *Bmpr1a* were among the significantly differentially expressed genes. Expression trends were verified by RT-qPCR and were consistent with RNA-seq data. To validate transcriptomic findings, Müller glia (MG) cultures were assessed for cell cycle re-entry and progenitor marker expression via immunocytochemistry (ICC) following treatment with conditioned media from PNU-282987- or DMSO-treated RPE cells. MG cells were exposed to conditioned media for 48 hours ($n = 3$ per condition). ICC was performed using primary antibodies against Nestin, Chx10/Vsx2, Pax6, and Ki67, followed by fluorescent secondary antibodies to quantify progenitor cells. Compared to DMSO control, cells labeling with Otx1/2, Chx10/Vsx2, and Ki67 were all found to be significantly increased after PNU-282987 treatment ($11.92\% \pm 1.45$, $p=0.00012$; $14.10\% \pm 0.1000$, $p=0.0045$; $46.13\% \pm 10.50$, $p=0.048$; respectively). These data further our understanding of the transcriptomic events underlying PNU-282987 treatment and verify that the $\alpha 7$ nAChR agonist can create progenitor-like cells in primary cultures. Future studies will utilize genetic manipulation and chemical antagonists to evaluate which of the highly enriched pathways identified by RNA-seq contribute to PNU-282987's neurogenic effect.

Disclosures: H.K. Vanzo-Sparks: None. D.M. Linn: None. C.L. Linn: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.18/K12

Topic: E.06. Vision

Support: DoD Grant# VR220084

Title: Dose-dependent stimulation of primary pig retinal pigment epithelium with PNU-282987 induces neurogenesis in primary pig retinal cell culture: Evidence from Ki67 staining

Authors: *D. M. LINN¹, S. WARNER¹, E. VAN PELT¹, T. SABER¹, C. L. LINN²;

¹Biomed. Sci., Grand Valley State Univ., Allendale, MI; ²Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Recent work has shown that activation of $\alpha 7$ nAChRs in adult mammals can lead to the generation of new retinal neurons. Previous studies have hypothesized that activation of $\alpha 7$ nAChRs on retinal pigment epithelial cells (RPE) with the selective $\alpha 7$ nAChR agonist, PNU-282987, induces the release of signaling molecules that cause retinal Muller glia to re-enter the cell cycle and produce progenitor cells that differentiate into new retinal cells. We have developed a 'high-throughput' protocol to expand on these earlier *in vivo* rodent studies by using primary cultures of adult pig RPE and retina. For this study, RPE were isolated and cultured with different concentrations of PNU-282987. After two days in culture, the RPE were rinsed and transferred to a separate culture dish containing isolated retinal cells. RPE were allowed to incubate with retinal cells for five days and cell numbers were quantified. We observed a significant increase in the number of retinal cells when co-cultured with RPE (without agonist), and a dose-dependent increase in cell numbers when RPE were exposed to increasing concentrations of PNU-282987. When retinal cells were co-cultured with primary RPE that were not exposed to PNU-282987, we observed a 28.3% increase ($p = 0.02$, $N=6$) over the five days. When PNU-282987 was applied, a threshold dose of 10 nM was observed. The maximal response occurred when concentrations between 200 and 500 nM were applied; consistent with previous studies using cultured rodent retinal cells that produced a maximal increase of 102.8% ($p < 0.001$, $N=6$). Additional experiments were conducted with the selective $\alpha 7$ antagonists, α -BTX (100 nM) and MLA (100 nM). When these selective blockers were added to the RPE cultures prior to exposure with PNU-282987, there was no significant difference in cell numbers when compared to unexposed RPE. To verify that proliferation of new cells occurred using PNU-282987, IHC studies using antibodies against Ki67 were conducted. Ki67 labeling also showed a dose dependent relationship with exposure to the $\alpha 7$ agonist. No Ki67 staining was observed at concentrations below 100 nM. At 100 nM, staining typically displayed 'spindle'-shaped profiles, while 200 nM showed more complex, 'stellate'-shaped profiles with dendritic branching. Less Ki67 staining was observed at 500 nM. Here we confirm an earlier report, where control and stimulated primary RPE can induce an increase in a primary retinal cell culture numbers from an adult non-rodent mammal in a dose-dependent, receptor-selective manner. Further experiments need to be conducted to confirm and expand on the Ki67 evidence supporting proliferative mechanisms activated via $\alpha 7$ nAChRs.

Disclosures: D.M. Linn: None. S. Warner: None. E. Van Pelt: None. T. Saber: None. C.L. Linn: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.19/K13

Topic: E.06. Vision

Support: NIH funding for intramural research ZIAHD000713 (RDF)

Title: Non-synaptic mechanism of ocular dominance plasticity

Authors: M. FOOTE¹, W. HUFFMAN³, E. SANTOS⁴, P. LEE¹, W. LI⁵, J. BONIFACINO⁶, *R. FIELDS²;

¹Natl. Inst. of Helth, Bethesda, MD; ²Natl. Inst. of Helth, Bethesda, United States Minor Outlying Islands; ³NICHD, Silver Spring, MD; ⁴NIH, Portland, OR; ⁵Natl. Eye Inst., Natl. Inst. Hlth., Bethesda, MD; ⁶Neurosciences and Cell. and Structural Biol. Div., Eunice Kennedy Shriver Natl. Inst. of Child Hlth. an, Bethesda, MD

Abstract: Experiments involving monocular and binocular deprivation laid the groundwork for understanding synaptic plasticity driven by coincident activation of pre- and postsynaptic neurons. An implicit assumption in these studies is that conduction velocity from both eyes is unaffected by visual experiences. Recent research showing that activity-dependent plasticity of myelin and node of Ranvier structure can alter conduction velocity requires tests to determine whether visual deprivation alters conduction velocity and node of Ranvier structure in the optic nerve and tract.

We induced monocular inhibition (MI) by inhibiting action potential firing in retinal ganglion axons, and monocular deprivation (MD) by eyelid suture in adult mice. MI was produced in Vglut2-CRE mice through overexpression of *Kir2.1* in retinal ganglion cells (p40-p100). WT mice were subjected to MD by monocular eyelid suture (p40-p100). Subsequently, we harvested optic nerves and tracts at p100 for immunohistochemical analysis of nodes of Ranvier (NOR) and measured the NOR gap lengths by confocal microscopy. Myelin thickness was measured by electron microscopy. Pattern visually evoked potential measurements in visual cortex and electroretinogram measurements were used to assess efficacy of MI and the latency of spike time arrival in visual cortex.

The results show that both MD and MI induce activity-dependent alterations in the NOR morphology of adult mice along the visual pathway. MD produced significant changes in spike time arrival latencies. Given the critical role of spike timing and neural synchrony in synaptic plasticity, activity-dependent plasticity of myelin will influence ocular dominance plasticity, adding a new layer to the synaptic plasticity paradigm initially described by Hubel and Wiesel. This non-synaptic activity-dependent plasticity would be relevant beyond the visual system, potentially influencing nervous system plasticity in other neural circuits during periods of learning, repair, and responses to changes in neural activity.

Disclosures: M. Foote: None. W. Huffman: None. E. Santos: None. P. Lee: None. W. Li: None. J. Bonifacino: None. R. Fields: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.20/K14

Topic: E.06. Vision

Title: Short-term monocular deprivation induces interocular dynamics in adult amblyopia

Authors: *D. Y. TS'O¹, A. W. ROE², R. M. FRIEDMAN³, M. M. CHERNOV³, M. QIAN², V. E. DAS⁴, Y. M. CHINO⁴;

¹Upstate Med. Univ., Syracuse, NY; ²Div. of Translational Neurosci., Nathan Kline Inst. for Psychiatric Res., New York, NY; ³Oregon Hlth. & Sci. Univ. - ONPRC, Beaverton, OR; ⁴Univ. of Houston Col. of Optometry, Houston, TX

Abstract: Normal interocular balance, the relative strengths of left and right eye inputs to the central visual pathways, is an important prerequisite for normal binocular vision. Human psychophysical studies have demonstrated a disruption of interocular balance following a period of short-term (1-3 hours) monocular deprivation (STMD). The unexpected outcome of STMD is a relative increase, not decrease, in the deprived eye (DE) gain post-STMD. This example of adult neural plasticity is opposite in sign to that expected by traditional monocular eye-patching for amblyopic treatment, and is apparently homeostatic rather than Hebbian in nature. We have previously conducted functional optical imaging (IOI) STMD studies in V1 of adult macaque monkeys, demonstrating an increased V1 response to DE stimuli relative to non-deprived eye (NDE) stimuli after STMD, and a shift in the stimulus-driven response baseline of the V1 ocular dominance columns (ODCs). These studies also revealed an active cooperative binocular mechanism that apparently seeks to maintain a highly spatially-regular left/right (L-R) eye opponency within the ODC framework. Leveraging the STMD response for the treatment of human amblyopia has shown some initial promise. Amblyopia represents an extreme chronic shift in interocular balance, generally of developmental origins. We sought to investigate the impact of amblyopia on the homeostatic STMD response. In an anisometropic amblyopic monkey, employing these same IOI methods. V1 activation and the ODC responses were observed to be dominated by the fellow eye and there was little evidence for binocular summation. Nevertheless, when the amblyopic eye was patched for 3 hours, there was a relative post-patch strengthening of its contribution to the ODCs, lasting 30 minutes. Overall, we found an STMD response in the ODCs of V1, as well as the L-R opponency similar to normals. In a strabismic amblyopic monkey however, preliminary analysis showed a near absence of the STMD response, as well as a reduction in L-R opponency. These preliminary results indicate a greater degree of binocular interaction and cooperativity in V1 of the anisometropic as compared with the strabismic amblyope, and also suggest that the neural mechanisms underlying the V1 STMD homeostatic response are embedded in the V1 binocular circuitry.

Disclosures: D.Y. Ts'o: A. Employment/Salary (full or part-time): SUNY Upstate Medical University. A.W. Roe: None. R.M. Friedman: None. M.M. Chernov: None. M. Qian: None. V.E. Das: None. Y.M. Chino: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.21/K15

Topic: E.06. Vision

Support: UNAM-DGAPA IN213423

Title: Detection of white matter degeneration of the visual pathway via diffusion-weighted MRI

Authors: *D. COUTIÑO¹, J. GUERRERO ZAVALA², M. GARCIA GUILLEN³, S. THEBAULT⁴, L. CONCHA⁵;

¹Neurobiologia, Univ. Nacional Autonoma de México, Queretaro, Mexico; ²Neurobiologia, Univ. Nacional Autonoma de Mexico, México, Mexico; ³Neurobiologia, Univ. Nacional Autonoma de Mexico, Queretaro, Mexico; ⁴Neurobiologia, Univ. Nacional Autonoma De México, queretaro de arteaga, Mexico; ⁵Neurobiologia, Univ. Nacional Autonoma De Mexico, Queretaro, Mexico

Abstract: Background. Diffusion MRI (dMRI) is a valuable non-invasive method for assessing the microstructural properties of brain tissue. However, its reliability diminishes in regions with complex fiber architecture, such as regions with fiber crossing. Previous studies in rodent models have validated advanced dMRI techniques for analyzing metrics associated with axonal density and have demonstrated their sensitivity to axonal degeneration (Rojas-Vite, 2019). We evaluated the sensitivity of advanced dMRI to detect axonal degeneration in vivo using asymmetric glaucoma as a model of localized white matter loss. Methods. We scanned 31 control subjects and 31 patients with asymmetric glaucoma recruited at the Instituto Mexicano de Oftalmología (IMO) using a 3T General Electric (GE) scanner. T1-weighted images were acquired at 0.8 mm isotropic resolution. dMRI data (1.7 mm³) included 6 b=0 s/mm² volumes and 16/32/64 diffusion-weighted volumes at b=800, 1500, and 2500 s/mm², respectively. At the optic nerve, DTI (Basser et al., 1994) was used to derive Fractional Anisotropy (FA) and Mean Diffusivity (MD). Constrained Spherical Deconvolution (CSD, Tournier et al., 2007) provided Apparent Fiber Density (AFD) and tractography of the optic nerves and chiasm, enabling bundle-wise quantification relative to the most affected eye. In the chiasm, Multi-Resolution Discrete Search (MRDS, Coronado-Leija et al., 2017) yielded voxel- and bundle-wise FA and MD. Fixel-Based Analysis (FBA, Raffelt et al., 2017) quantified Fiber Density (FD), Cross-Section (FC), and their combination (FDC) across the visual pathway. Diffusion metrics were correlated with clinical indicators: Retinal Nerve Fiber Layer (RNFL) thickness, vertical cup-to-disc ratio (vCD), and visual field mean deviation (MD). Results. Controls showed no asymmetries. In glaucoma, affected nerves had reduced FA and AFD, and higher MD than contralateral nerves and controls.

In the chiasm, FA, MD, and AFD showed asymmetries; only FA differed significantly between groups. FBA revealed widespread FD, FC, and FDC reductions in patients. MD correlated with vCD ($r=0.687$, $p<0.001$), AFD with visual field MD ($r=0.576$, $p=0.005$), and FD with RNFL thickness ($r=0.473$, $p=0.01$). Conclusions. Advanced dMRI analysis methods are sensitive enough to detect microstructural changes associated with neurodegeneration in regions of complex configuration such as crossing fibers. Moreover, the strong correlations between diffusion-derived metrics and clinical parameters support the validity of dMRI as a non-invasive tool for characterizing white matter damage in vivo.

Disclosures: D. Coutiño: None. J. Guerrero Zavala: None. M. Garcia Guillen: None. S. Thebault: None. L. Concha: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.22/K16

Topic: E.06. Vision

Support: NEI Grant R01EY031589

Title: Changes in the healthy brain as a result of simulated central vision loss

Authors: *P. DEMIRAYAK¹, P. STEWART², M. MANIGLIA⁴, S. JAYAKUMAR⁴, E. CUTTS³, M. RAGLAND⁵, J. MUNNEKE⁶, N. B. TURK-BROWNE^{8,9}, A. SEITZ⁷, K. M. VISSCHER¹⁰;

¹Neurobio., Univ. of Alabama, Birmingham, Birmingham, AL; ²Univ. of Alabama, Birmingham, Homewood, AL; ³Univ. of Alabama, Birmingham, Birmingham, AL; ⁴Univ. of California at Riverside, Riverside, CA; ⁵Univ. of Alabama at Birmingham, Birmingham, AL; ⁶Psychology, ⁷Psychology, Art&Design, Communication and Speech Disorders, Northeastern Univ., Boston, MA; ⁸Psychology, Yale Univ., New Haven, CT; ⁹Wu Tsai Institute, Yale Univ., New Haven, CT; ¹⁰Neurobio., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: In response to the loss of central vision, individuals typically adopt an alternative fixation strategy, relying on a peripheral retinal area—the preferred retinal locus (PRL)—to process fine visual details. This results in marked changes in the daily experiences of people with central vision loss and is a strong example of perceptual learning in real life. Perceptual learning offers a powerful framework for examining experience-dependent neural plasticity, making it particularly relevant for studying adaptations following central vision loss. To simulate the visual experience of central vision loss in healthy individuals, we employed a gaze-contingent display paradigm that artificially occludes central vision. Our approach aims to contribute better understanding of the plasticity in brain function associated with compensation following central vision loss. Each participant was assigned a “trained PRL location” in either the left or right peripheral visual field along the horizontal meridian. The study enrolled healthy adults with

normal or corrected-to-normal vision who were exposed to visual conditions mimicking central vision loss. Participants completed 20 visual training sessions and underwent MRI scans before and after training. During each MRI session, we acquired functional data while participants performed orientation discrimination and contour integration tasks. We assessed BOLD responses to trials of these tasks before and after visual training in healthy vision individuals. Consistent with the literature, we observed a brain-wide decrease in activity after training. This pattern is consistent with increased neural efficiency in visual processing. In contrast, however, the dorsolateral prefrontal cortex, lateral parietal cortex, and posterior midline regions showed increased activity after training. We are currently evaluating whether these increases reflect training of cognitive control and/or other mechanisms. Our study contributes to understanding how the brain compensates for central vision loss and provides insight into patterns of experience-dependent neural plasticity in healthy adults.

Disclosures: P. Demirayak: None. P. Stewart: None. M. Maniglia: None. S. Jayakumar: None. E. Cutts: None. M. Ragland: None. J. Munneke: None. N.B. Turk-Browne: None. A. Seitz: None. K.M. Visscher: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.23/Web Only

Topic: E.06. Vision

Title: Neuroimaging Insights into the Longitudinal Corticalization of the Human Visual System

Authors: J. WANDERLEY SOARES DE VIVEIROS¹, *N. D'IVANENKO², R. PITZ FONSECA GUIMARÃES³, N. SILVA⁴, M. QUEIROZ⁵, G. NOBRE NOGUEIRA⁶, D. MARRONE CORREIA DE REZENDE⁷, G. BITOLO⁸, G. WAGNER BARATTI ROCHA¹¹, A. FERNANDES RODRIGUES DA CUNHA DE ALMEIDA¹², A. OLIVEIRA MAFRA¹³, L. SILVA MOURA DORNELES¹⁴, R. GARDONI LOPES MARTINS DE BRITO¹⁵, C. AQUINO PEREIRA LIMA⁸, V. BASTOS¹⁶, G. LOPES DA SILVA⁹, I. DUTRA BARBOSA¹⁴, J. FERREIRA COSTA⁸, A. NUNES DE SOUSA¹⁷, A. GOMES¹⁸, S. SILVA¹⁰, M. SCHVINN¹⁹, L. IMAI¹³, M. RUIZ CARRASCOSA²⁰, M. HASS DAS EIRAS⁹, A. BONIFÁCIO⁹, M. CORRÊA GONDIM BEZERRA RODRIGUES²¹, P. HENRIQUE ABBADE MENDES¹³, R. FERNANDES GONÇALVES²²;

¹Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte, Brazil; ²Univ. Nove de Julho, São Bernardo do Campo, Brazil; ³Ctr. Universitário UniFacig, Manhuaçu, Brazil; ⁴Univ. Federal da Paraíba, João Pessoa, Brazil; ⁵Univ. José do Rosário Vellano (Unifenas), Belo Horizonte, Brazil; ⁶Univ. Federal do Ceará (UFC), Fortaleza, Brazil; ⁷Univ. Federal de Mato Grosso, Cuiabá, Brazil; ⁸Univ. Nove de Julho (UNINOVE), São Bernardo do Campo, Brazil; ⁹Univ. Nove de Julho (UNINOVE), Osasco, Brazil; ¹⁰Univ. Nove de Julho (UNINOVE), Guarulhos, Brazil; ¹¹Univ. Estadual de Campinas (UNICAMP), Campinas, Brazil; ¹²Univ. Iguazu (UNIG), Nova Iguaçu, Brazil; ¹³Univ. Santo Amaro - Campus I (UNISA), São Paulo, Brazil; ¹⁴Pontifícia

Univ. Católica de Minas Gerais Campus Betim (PUCMG), Betim, Brazil; ¹⁵Faculdade Ciências Médicas de Minas Gerais (FCMMG), Belo Horizonte, Brazil; ¹⁶Univ. Federal de Juiz de Fora (UFJF), Juiz de Fora, Brazil; ¹⁷Univ. Estadual da Região Tocantina do Maranhão (UEMASUL), Imperatriz, Brazil; ¹⁸Ctr. Universitário Christus (Unichristus), Fortaleza, Brazil; ¹⁹Faculdades Pequeno Príncipe (FPP), Curitiba, Brazil; ²⁰Pontifícia Univ. Católica do Paraná (PUCPR), Londrina, Brazil; ²¹Ctr. Universitário Maurício de Nassau (Uninassau), Recife, Brazil; ²²Faculdade Evangélica Mackenzie do Paraná (FEMPAR), Curitiba, Brazil

Abstract: The human primary visual cortex (V1) undergoes multiphasic development, integrating structural maturation, functional organization, and connectivity, all fundamental for building visual perception and cognition. This study aimed to systematically review the available evidence on human V1 development, focusing on findings from neuroimaging, electrophysiology, and functional connectivity, while also highlighting clinical implications. Following PRISMA guidelines, we searched *PubMed*, *Cochrane* and *Embase* databases. We included 25 original human studies, covering techniques such as structural and functional magnetic resonance imaging, MAP-MRI, EEG, and functional connectivity analyses. Our main findings demonstrate that V1 exhibits early maturation of cortical layers and myelination in the first months of life, with progression persisting into adolescence, pointing to a prolonged critical period of plasticity. MAP-MRI studies identified the precise definition of areal boundaries and lamination patterns, which are crucial for functional specialization. fMRI data revealed that higher-order visual areas undergo cortical recycling processes, allowing for specialization in face and word recognition, with evidence of retraction in less-demanded areas. Functional connectivity analyses showed early modularity within V1, alongside a significant expansion of local association fibers during childhood and adolescence, as well as increased multisensory integration, suggesting an adaptive mechanism to environmental demands. EEG data indicated a correlation between C1 component latency and V1 cortical volume, underscoring the relationship between structural maturation and functional specialization. Cases of congenital visual deprivation exhibited remarkable anatomical reorganization in V1, involving the strengthening of alternative connections and the recruitment of associative regions. This highlights both cortical plasticity and the potential for early intervention during critical periods. These results reinforce that V1 development is guided by intrinsic mechanisms modulated by sensory experience, strengthening the relevance of therapeutic strategies for visual neurodevelopmental disorders and offering insights into individual trajectories of cortical plasticity.

Disclosures: J. Wanderley Soares de Viveiros: None. N. D'ivanenko: None. R. Pitzr Fonseca Guimarães: None. N. Silva: None. M. Queiroz: None. G. Nobre Nogueira: None. D. Marrone Correia de Rezende: None. G. Bitolo: None. G. Wagner Baratti Rocha: None. A. Fernandes Rodrigues da Cunha de Almeida: None. A. Oliveira Mafra: None. L. Silva Moura Dorneles: None. R. Gardoni Lopes Martins de Brito: None. C. Aquino pereira lima: None. V. Bastos: None. G. Lopes da Silva: None. I. Dutra Barbosa: None. J. Ferreira Costa: None. A. Nunes de Sousa: None. A. Gomes: None. S. Silva: None. M. Schvinn: None. L. Imai: None. M. Ruiz Carrascosa: None. M. Hass das Eiras: None. A. Bonifácio: None. M. Corrêa Gondim Bezerra Rodrigues: None. P. Henrique Abbade Mendes: None. R. Fernandes Gonçalves: None.

Poster

PSTR025: Visual System: Plasticity and Repair

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR025.24/L1

Topic: E.06. Vision

Support: Natural Science Foundation of China Grant NSFC32271081
Natural Science Foundation of China Grant NSFC32200857
China Postdoctoral Science Foundation Grant 2022T150021
National Science and Technology Innovation 2030-Major Project
2022ZD0204803
China Postdoctoral Science Foundation Grant 2023M740125

Title: The formation of word-selective areas in macaque IT cortex through visual experience

Authors: *J. YANG¹, H. YAO², K. WANG¹, J. LUO¹, S. TANG¹, Z.-L. LU⁴, P. BAO³;
¹Peking Univ., Beijing, China; ²Peking Univ., Beijing, China; ³Peking Univ., Peking, China;
⁴New York Univ. Ctr. For Neural Sci., New York, NY

Abstract: The emergence of word-selective regions in the human brain, such as the visual word form area (VWFA), depends on visual experience, yet how visual experience shapes the formation of category-selective areas remain unclear. Here, two macaques passively viewed Chinese characters while widefield calcium imaging was performed across ~20 sessions. Thirty characters were randomly paired with 1, 2, or 3 drops of juice, and each session introduced ten novel characters associated with a single drop. Training led to enhanced responses to trained words, along with a pronounced expansion of word-selective regions, mirroring the rapid development of word-selective areas in humans. Contrary to the prevailing view of manifold shrinkage in learning, representational similarity analysis (RSA) showed that learning a novel category increased both between- and within-word distances, particularly in newly emergent word-selective regions. The tuning and geometric changes led to greater information capacity and higher discriminability, as evidenced by increased Fisher information, mutual information, and word discrimination performance. All effects were strongly modulated by reward strength, being most pronounced for the ten most rewarded characters, and were negligible for untrained control characters. Taken together, these findings highlight that repeated exposure to a novel category, especially with strong reinforcement, rapidly drives the formation of category-selective regions by boosting neural responses and reorganizing representational geometry.

Disclosures: J. Yang: None. H. Yao: None. K. Wang: None. J. Luo: None. S. Tang: None. Z. Lu: None. P. Bao: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.01/L2

Topic: F.04. Voluntary Movements

Title: Increased alpha band activity in motor areas during involuntary errors in a bimanual typing task

Authors: *T. HASHIMOTO¹, S. IWAMA², J. USHIBA³;

¹Keio Univ., Suntougun, Japan; ²Grad. Sch. of Sci. and Technol., Keio Univ., Yokohama, Japan;

³Keio Univ., Kanagawa, Japan

Abstract: Bimanual movements in activities of daily living (ADLs), such as cooking and desk work, involve asynchronous but coordinated actions of both hands. Previous studies have investigated neural signatures during bimanual tasks through electroencephalogram (EEG) recordings. However, most of them focused on simple, synchronous hand movements that do not reflect ADLs. Moreover, EEG changes associated with involuntary motor errors in such tasks remain unclear. In the present study, we examined whole-head EEG activities associated with involuntary errors while performing a complex motor task that requires asynchronous bimanual key typing. Thirty healthy adult participants performed the typing task involving a 20-second keystroke sequence. In this task, the participants pressed keys alternately with two fingers of each hand in a left-right sequence, paced by numbers presented at a fixed rate. The typing rate was adaptively controlled in real time to standardize the frequency of involuntary motor errors across participants, according to their keystroke performance. Keystroke timing and accuracy were analyzed. EEG time-frequency analysis identified alpha (8-13 Hz) and beta (14-30 Hz) bands event-related desynchronization (ERD) localized to sensorimotor cortex during the movement. To identify brain regions and EEG frequency bands associated with keystroke errors, permutation tests were conducted on EEG amplitudes in the alpha and beta bands within one second of keystroke errors (when the correct keystroke was not made within a defined time window) across all participants. EEG amplitudes were normalized to the average value of the resting state preceding the movement onset. The analysis showed a significant increase in alpha band amplitude around sensorimotor cortex during keystroke errors compared to time windows randomly selected during the same trials ($p < 0.05$). These results indicate that increased alpha band activity in motor-related cortical areas is a noninvasive biomarker of involuntary motor errors, reflecting a reduction of ERD specific to bimanual movement. They further suggest that the alpha band activity in sensorimotor cortex could be targeted in future neurofeedback or neuromodulation protocols designed to predict and prevent involuntary motor errors during bimanual movement.

Disclosures: T. Hashimoto: None. S. Iwama: None. J. Ushiba: A. Employment/Salary (full or part-time): A representative director of LIFESCAPES Inc., receiving a salary and holding shares in the company, in which this research did not receive any equipment, financial support, or human resources..

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.02/L3

Topic: F.04. Voluntary Movements

Support: NSF Grant 1940950

Title: Restricting the search space using robotics hinders motor learning

Authors: *N. SHIN, R. RANGANATHAN;
Michigan State Univ., East Lansing, MI

Abstract: Learning to control movements is particularly challenging in systems with many degrees of freedom, a situation known as the degrees of freedom (DoF) problem. With multiple variables at multiple levels, ranging from joints and muscles to neural control, contributing to the same goal, learners must search through a high-dimensional space to find effective solutions. As the number of DoF increases, the search space expands rapidly, highlighting the need for strategies that reduce the dimensionality to facilitate motor learning. This study explores how explicitly limiting motion in selective DoF using robotics can reduce this search space and potentially facilitate more efficient motor learning. Participants completed a two-dimensional cursor control task wearing a cyber glove, aiming to match a target using finger movements. They were randomly assigned to one of two groups; 1) in the restricted group, a haptic glove applied resistance to restrict the movement of uninvolved fingers that did not contribute to cursor movement in the target direction, thus constraining the degrees of freedom in the search space, and 2) in the control group, participants performed the task without any movement restrictions, allowing free exploration of the entire search space. Both groups completed one block of pre-test without resistance, six blocks of training either with or without resistance according to group assignment, and one block of post-test without resistance. A manipulation check confirmed that the variance in uninvolved fingers was significantly lower in the restricted group, indicating that the glove successfully restricted their movement. Both groups demonstrated improved task performance, as evidenced by reduced completion times. However, the restricted group took longer than the control group to complete the task in the post-test after the resistance was removed. Additionally, the restricted group exhibited lower movement efficiency, as evidenced by more deviated trajectories from the straight line between the home position and the target position. These findings suggest that constraining degrees of freedom in the search space may not benefit motor learning in redundant tasks. While both groups improved their performance, the restricted group showed a longer completion time and reduced movement efficiency. This supports the guidance hypothesis, which suggests that excessive guidance can lead learners to rely on external assistance rather than developing independent control. The results indicate that reducing the search space was less effective for skill acquisition than allowing free exploration.

Disclosures: N. Shin: None. R. Ranganathan: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.03/L4

Topic: F.04. Voluntary Movements

Support: NSF HCC 2133879
Shriners Childrens Research Grant 79139-NCA-23

Title: Classifying Missing Hand Grasp Motions from Ultrasound Image Statistics in Children with Congenital Limb Absence

Authors: *S. A. WARAICH¹, E. WINSLOW², J. FITZGERALD⁴, W. M. JOINER³, J. SCHOFIELD⁵;

¹Mechanical and Aerospace Engin., ²Biomed. Engin., ³Dept. of Neurobiology, Physiol. and Behavior, Univ. of California, Davis, Davis, CA; ⁴Biomed. Engin., ⁵Mechanical and Aerospace Engin., UC Davis, Davis, CA

Abstract: Children with congenital below-elbow limb deficiency often face barriers to using advanced prosthetic hands due to unintuitive control systems and limited pediatric-specific options. Our prior work demonstrated that muscle deformation patterns captured via ultrasound imaging can classify intended hand grasps in this population. However, such models typically rely on high-dimensional feature sets, which may limit feasibility for real-time control. Here, we evaluate whether a lower-dimensional, interpretable set of image-derived features can classify grasp intention with comparable accuracy. Ultrasound data were collected from 30 children (ages 5-20) as they attempted performing 10 distinct hand grasps with their absent limb. For each trial, we extracted frame-wise differences in muscle deformation and computed 10 local image statistics, derived from multipoint spatial correlations among neighboring pixels. Each ultrasound image was divided into a grid of square patches, and statistics were computed within each patch to preserve local structure. These statistics - originally developed to probe mid-level visual processing in human participants - provide a compact, interpretable representation of image structure while reducing feature dimensionality. We trained and tested machine learning classifiers to assess grasp classification performance. Principal component analysis (PCA) revealed more grasp-related structure in features from the intact limb compared to the residual limb. Individual image statistics calculated from 64 patches of the residual limb achieved classification accuracies between 56% and 87% (chance = 10%). Accuracy increased with more patches (4-100), plateauing around 36-49. Combining multiple statistics did not improve performance, suggesting a small number of localized, low-dimensional features may suffice to decode grasp intent. While classification accuracy requires improvement, our preliminary findings suggest that it may be feasible to use a relatively low-dimensional set of features for pediatric ultrasound-based control systems for prosthetic devices.

Disclosures: S.A. Waraich: None. E. Winslow: None. J. Fitzgerald: None. W.M. Joiner: None. J. Schofield: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.04/L5

Topic: F.04. Voluntary Movements

Support: JST SPRING JPMJSP2123
JST Moonshot R&D (JPMJMS2012)

Title: Pupil-linked arousal mediates reward-related changes in motor performance

Authors: *N. SENTA¹, J. USHIBA², M. TAKEMI³;

¹Grad. Sch. of Sci. and Technol., ²Fac. of Sci. and Technol., Keio Univ., Yokohama, Japan;

³Grad. Sch. of Advanced Sci. and Engin., Hiroshima Univ., Higashihiroshima, Japan

Abstract: Arousal adjusts neural gains that determine how we perceive, decide, and move. Pupil diameter (PD) is a non-invasive proxy for this state and typically dilates as prospective reward increases and task difficulty rises, though both the direction and magnitude of such effects vary across contexts. Whether these two motivational factors interact at the level of pupil-linked arousal, and how the resulting state influences motor behavior, remains unclear. Here, we addressed these questions in 23 healthy adults who performed an eight-item finger-tapping sequence as quickly and accurately as possible. In each trial, one of three predefined sequences was used, and participants were informed of the upcoming sequence via premovement cues. Each sequence was practiced across 96 trials. In the test phase, varying reward amounts (0, 500, or 2,500 Japanese yen) and difficulty levels (easy, moderate, hard) were indicated by premovement cues. Task difficulty was manipulated by adjusting the time allowed to complete the sequence. PD was recorded during the test phase and averaged around movement onset. A two-way repeated-measures ANOVA tested the interaction between reward and difficulty on PD, revealing a significant main effect of reward ($p < .05$) but no effect of difficulty and no interaction. We then fitted a Bayesian generalized linear mixed model that jointly predicted (i) binary performance from reward, difficulty, PD (linear and quadratic terms), and (ii) PD from reward and difficulty, with by-participant random intercepts. Results showed that larger reward amounts improved success probability (500 yen: 95% Credible Interval [0.02, 0.42]; 2,500 yen: [0.17, 0.58]), while higher difficulty impaired it (moderate: [-0.86, -0.46]; hard: [-1.25, -0.85]). Rewards also enlarged PD (500 yen: [0.04, 0.07]; 2,500 yen: [0.10, 0.14]), while difficulty had no credible effect on PD (moderate: [-0.00, 0.03]; hard: [-0.03, 0.00]). Crucially, greater PD was linearly associated with poor performance [-10.27, -1.56]. While the model included a positive quadratic term [0.10, 1.30], its effect was modest, producing only a shallow upward curvature at high arousal levels. Thus, we found no compelling evidence for a Yerkes-Dodson inverted U-shaped relationship in this motor task. Instead, reward influences motor performance both directly and indirectly via pupil-linked arousal, while difficulty impairs performance independently of arousal. The arousal-performance relationship was primarily monotonic and negatively sloped with limited curvilinear modulation.

Disclosures: N. Senta: None. J. Ushiba: A. Employment/Salary (full or part-time): A representative director of LIFESCAPES Inc., receiving a salary and holding shares in the

company, in which this research did not receive any equipment, financial support, or human resources.. **M. Takemi:** None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.05/L6

Topic: F.04. Voluntary Movements

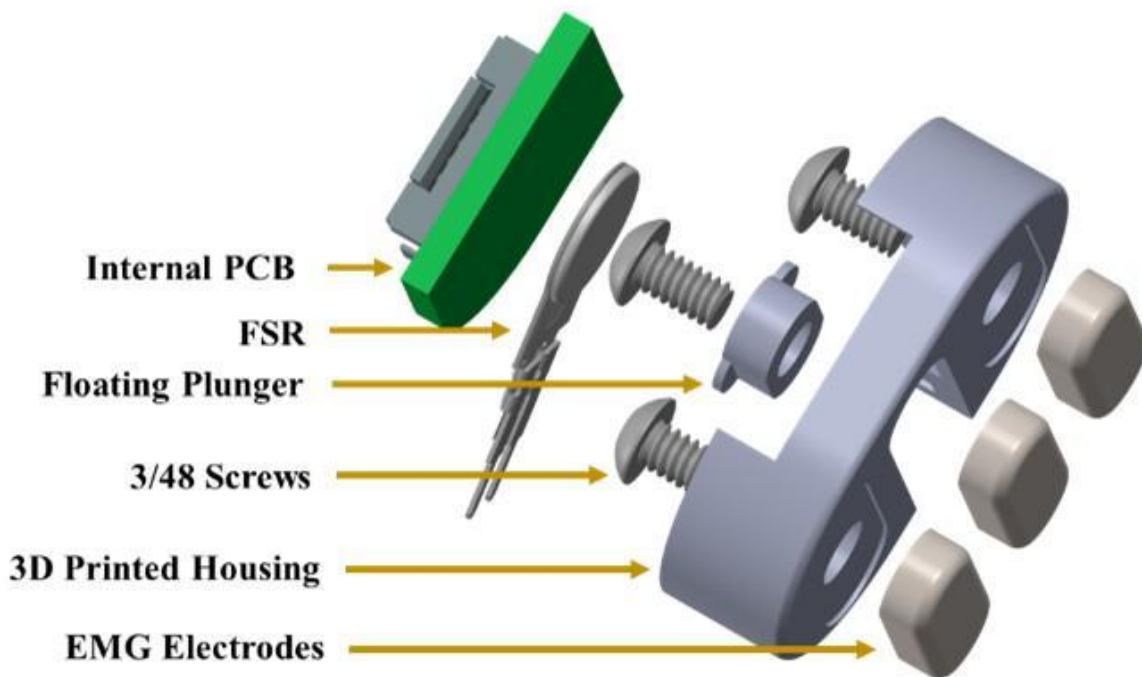
Support: NSF GRFP 2036201
NSF NRT Award 2152260

Title: The Development of a Multi-Modal Electromyography and Force Myography Sensor for Upper Limb Prosthesis Control

Authors: ***P. YOUNG**¹, M. BATTEW³, M. FINLEY², J. SCHOFIELD¹;

¹Mechanical and Aerospace Engin., ²Univ. of California - Davis, Davis, CA; ³Dept. of Mechanical and Mechatronic Engin. and Advanced Manufacturing, California State University, Chico, Chico, CA

Abstract: Upper limb loss can significantly reduce quality of life by limiting a person's ability to perform daily activities independently. Upper limb prostheses are often prescribed to help restore lost function and improve autonomy. Modern mechatronic prostheses commonly use surface electromyography (EMG) sensors combined with pattern recognition algorithms to detect muscle activity in the residual limb and predict and execute the user's intended hand gestures. However, as EMG-based control systems rely on consistent muscle recordings, this technique suffers from limitations such as change in electrode readings when they shift or change contact with the limb resulting from variations in limb position or grasped loads. Force myography (FMG), an experimental control scheme that measures the volumetric change of the limb, has been combined with traditional EMG systems and has been shown to yield higher gesture classification accuracies, hinting at the fact that this combination could lead to more effective prosthesis control. However, most of these multi-modal systems are experimental and employ separate EMG and FMG systems or have a form factor that is larger than conventional EMG systems, both of which could limit the feasibility of prosthesis integration. This work presents a combined EMG+FMG sensor that is in the form factor of a 13E200 Myoback EMG sensor, a commercially available and widely used EMG sensor for advanced upper limb prosthesis control. Here, we present our design metrics along with the electrical and mechanical properties of this sensor. We then recruited n=8 able-bodied participants to statically perform 10 unique gestures along with a maximum voluntary contraction while wearing 8 of our EMG+FMG sensors to demonstrate our sensor's ability to accurately classify hand gestures. Using a linear discriminant analysis classifier paired with a 60-40 training-testing scheme, our results indicated an average classification accuracy of 99.8% for the EMG+FMG sensor illustrating its efficacy for gesture classification and feasibility for prosthesis integration.



Disclosures: P. Young: None. M. Battraw: None. M. Finley: None. J. Schofield: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.06/L7

Topic: F.04. Voluntary Movements

Support: NSF Grant 2211906

Title: Utilizing Motion Capture and Neural Networks to Extract Human Hand Kinematic Data

Authors: *H. KUMAGAI¹, J. MCGINNIS², K. HONG³, J. SCHOFIELD³, P. D. MARASCO⁴, R. WEIR⁵;

²Biomed. Engin., ³Mechanical and Aerospace Engin., ¹UC Davis, Davis, CA; ⁴Biomed. Engin., Cleveland Clinic, Lerner Res. Inst., Cleveland, OH; ⁵Anschutz Med. Campus, Univ. of Colorado, Denver, CO

Abstract: Humans have uniquely identifiable movement characteristics that allow for easy visual differentiation from contrasting movement patterns, such as robotic movement. Within our hands, such movement characteristics include individualized joint angle trajectories among the digits, as well as the presence of biological noise (e.g., physiological tremor). Our work aims to quantify these values to develop a framework of human hand motion and a better understanding

of human motor control. We recruited 7 able-bodied participants with an average age of 25 (+/- 3) years old to perform a set of 4 common hand grasps (power, pinch, tripod, lateral pinch) while following a metronome at a fast and slow speed. Two GoPros were positioned around the participant's dominant hand to record multiple angles of their hand movement as participants repeated each hand grasp for 20 repetitions per speed. Using Google MediaPipe's HandLandmarker model, we extracted the hand landmarks from the footage and calculated kinematic and dynamic data using a custom Python script. We separated the movement data from the kinematic noise data using a time series decomposition method for isolated analysis of the two components. The resultant joint angle movement plots demonstrate the variability of human movement. Each participant's data shows similar joint angle movement patterns in the opening and closing of the hand, but the slopes of the joint angles over time and the mean angles are largely individualized among datasets. Furthermore, frequency distributions of the kinematic noise data demonstrate Gaussian behavior. As a result, we can understand and predict the presentation of biological noise in human movement in the context of joint angle changes over the duration of different hand gestures. Future work with this study should analyze the quantitative and qualitative effects on human embodiment when interacting with non-human interfaces that move in a humanistic manner (e.g., prosthetic limbs or virtual reality hands).

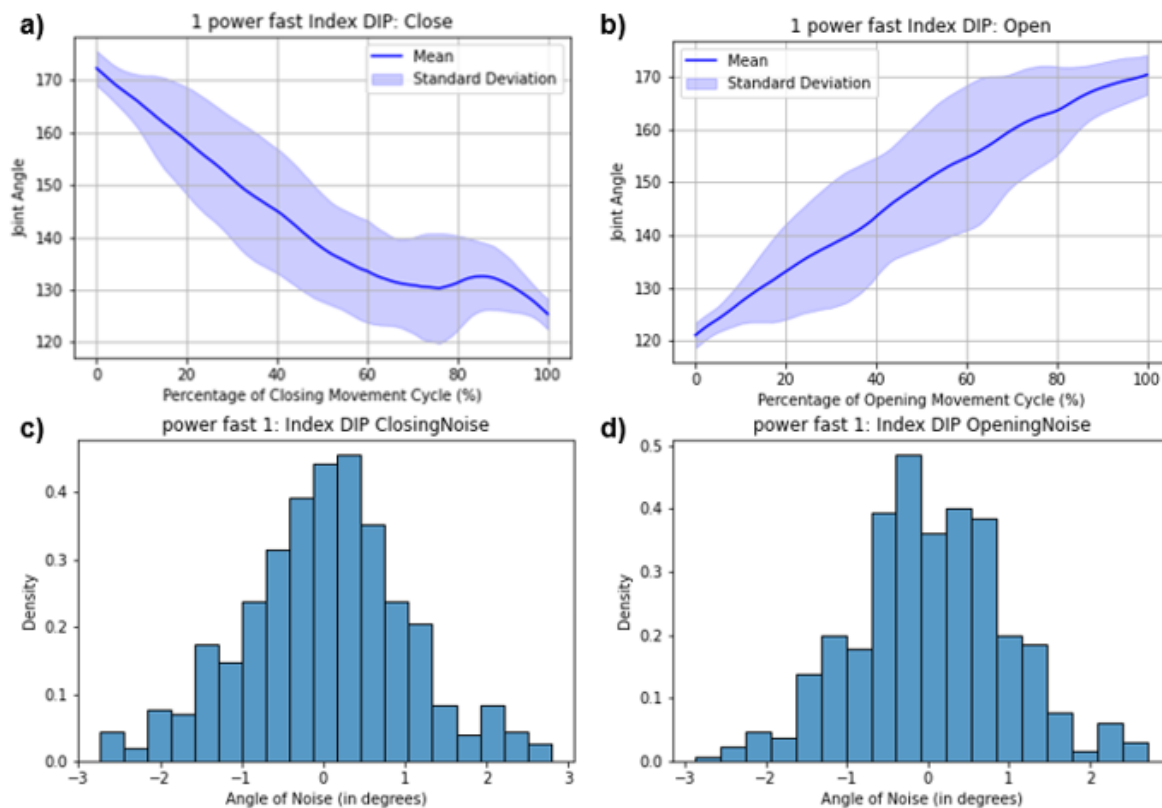


Figure 1: Joint Angle Movement Plots (a, b) and Extracted Kinematic Noise Density Plots (c, d) for Participant 1

Disclosures: H. Kumagai: None. J. McGinnis: None. K. Hong: None. J. Schofield: None. P.D. Marasco: None. R. Weir: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.07/L8

Topic: F.04. Voluntary Movements

Support: CUNY IRG 80209-11 26

Title: Performing a daily lifting task via phone-based VR task vs. reality conditions

Authors: *W. ZHANG^{1,2}, A. MOHAMED³, F. GU³, H. ZHENG¹, W. YANG¹, J. DIAZ¹;

¹Physical Therapy, Col. of Staten Island / City Univ. of NY, Staten Island, NY; ²Ctr. for Developmental Neurosci., Col. of Staten Island / City Univ. of NY, Staten Island, NY;

³Computer Sci., Col. of Staten Island, City Univ. of New York, Staten Island, NY

Abstract: Virtual reality (VR) has been utilized to simulate real-world tasks (Cinar et al., 2024; Iqbal et al., 2024) with regard to human movement control and functional evaluation and rehabilitation. Previous studies provided evidence for VR efficacy and usefulness in comparison with conventional training conditions in fields of motor learning (Anglin et al., 2017) and adaptation, gait analysis (De Keersmaecker et al., 2023), and fine motor function rehabilitation (Yeh et al., 2017). Although the usability of VR has been supported mostly by its attractive game-nature and motivated intent, it is still not clear the extent to which the virtual feedback impact on the sensorimotor integration thus eventually on the executive motor performance. In this study, we developed a novel smart phone APP as a virtual reality task to evaluate hand function and performance during daily object grasping and lifting manipulations. The APP, developed using the Unity game engine, capitalizes on the phone's built-in accelerometer and gyroscope sensors to record and analyze movement patterns with precision. We hypothesize that motor performance and motor learning if applied are similar in VR test to reality tasks. In addition, proportion of virtual feedback is associated with the accuracy of motor output performance. Twelve healthy adult subjects participated and performed three object lifting and transporting tasks, two of which are VR tasks (phone-VR task and TV-VR task) and one is conventional task (i.e., Real task). Subjects were instructed to grip and/or grasp, lift, transport and return an object by using three digits (thumb, index and middle fingers) for consecutive 10 times under each condition. The hand-held object manipulated during the task is either 1) a smartphone during VR tasks with visual feedback presented by the phone screen (phone-VR task) or with mirrored image of the phone to a TV screen (TV-VR task), or 2) a full-filled glass during Real task. Four 6-dimensional sensors (Ascension trakSTARTM) were attached to record three axes of position and orientation for the object and involved digits. Our results revealed significantly larger object tilting and higher cross-trial variability during VR tasks compared to Real task, regardless of grip width or virtual feedback proportion. These findings suggest that usage of VR maybe associated with delayed motor learning or reduced motor output performance, resulting from the absence of real-world physical consequences.

Disclosures: W. Zhang: None. F. Gu: None. H. Zheng: None. W. Yang: None. J. Diaz: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.08/L9

Topic: F.04. Voluntary Movements

Title: Perception and action decoupled in force estimation

Authors: *W. TANG, K. WEI;
Peking Univ., Beijing, China

Abstract: As a fundamental aspect of sensorimotor control, force perception is a unique type of perception since it involves both afferent and efferent cues. Quantification of force perception typically requires human participants to either verbally report the force magnitude (numeric judgment) or replicate the force (force matching) after a force production. However, whether these two perceptual measures, one is subjective rating and the other is a motor readout, unbiasedly reflect actual force production has not been systematically investigated. Here we examined force percepts over a wide range of force levels. After people make a sustained force (Exp1), their numeric judgment shows a substantial overestimate over a while range of target force levels. In contrast, force matching faithfully replicates the target forces. Interestingly, if people deal with a quick force pulse (Exp2), instead of a sustained force as in Exp1, their numeric judgment is less overestimated, but their force matching starts to show a central tendency (underestimation for large target forces and overestimation for small forces). We reason that numeric judgment of force is based on the comparison of desired force output (instantiated by efferent signals) and perceived force output, with the latter subject to sensory attenuation by motor prediction that has been previously implicated in force perception. Desired force is thus larger than the attenuated force estimate, and this positive “error” leads to the overestimation. Force pulse, with a shorter duration than sustained force, is less affected by sensory attenuation, thus leading to a reduction in overestimation. The central tendency effect in force matching is consistent with a Bayesian integration account of similar effects as in other percepts (e.g., timing perception and line length): sensory feedback of the target force, as a likelihood, is biased towards a central prior that is built upon the entire force history in the experimental session, resulting in a biased posterior estimate. Our findings highlight that perceptual and action systems diverge in force perception, and their biases reflect their respective multimodal cue combination in keeping with Bayesian rules.

Disclosures: W. Tang: None. K. Wei: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.09/L10

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI Grant Number 24K23805

Title: Passive Ligament and Tendon Structures Support Efficient Neuromuscular Control of Skilled Hand Movements

Authors: *T. ITO¹, T. KOKUBUN²;

¹Saitama Prefectural Univ., Koshigaya, Saitama, Japan; ²Physical Therapy, Saitama Prefectural Univ., Koshigaya-Shi, Japan

Abstract: Skillful hand movements rely on muscles, ligaments, and tendons, yet their integrated role in motor control remains unclear. Most studies focus on muscle activity, overlooking passive biomechanical contributions. This study investigated hand motor control by comprehensively analyzing muscle, ligament, and tendon contributions. Ten healthy young adults (5 males, 5 females, 22.2 ± 1.9 years, right-handed) participated. Right-hand kinematics and surface electromyography of flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) were recorded. Three experiments were conducted: (A) Index finger drawing circles as large as possible (5 trials) to evaluate collateral ligament restraint via metacarpophalangeal (MP) joint flexion/abduction relationships. (B) Passive wrist joint movements using Biodex to assess flexor tendon passive effects on MP joint. (C) Keyboard tapping (numbers 7 and 9, 30 cycles) analyzed for MP joint kinematics, fingertip trajectory, tapping time, and FDS/EDC ratio. Participants were categorized as FLEX or EXT based on whether MP joint was more often flexed or extended. Parameter differences were tested using t-test or Mann-Whitney U-test. This study was approved by the Ethical Review Committee (No. 21,518). (A) All participants showed elliptical fingertip trajectories; MP joint flexion(+)/abduction(+) demonstrated a significant negative correlation ($r=-0.48$, $p<0.01$, Pearson's). (B) Wrist dorsiflexion passively flexed MP joint (regression coefficient $b<0$, $p<0.01$). (C) All participants exhibited wrist dorsiflexion during tapping. FLEX showed greater MP joint flexion(+)/extension(-) angles than EXT (FLEX ($n=6$) vs. EXT ($n=4$): $6.4 \pm 4.6^\circ$ vs. $-4.6 \pm 5.6^\circ$, $p=0.01$, $d=1.90$) and a lower FDS/EDC ratio (0.6 ± 0.3 vs. 2.1 ± 1.3 , $p=0.04$, $d=1.35$) than EXT. No group differences in MP joint abduction(+)/adduction(-) angles ($-2.0 \pm 5.1^\circ$ vs. $2.2 \pm 2.2^\circ$, $p=0.20$, $d=0.90$), fingertip peak variability ($1.7 \pm 0.3\text{mm}$ vs. $2.1 \pm 0.8\text{mm}$, $p=0.30$, $d=0.72$), or tapping time ($0.3 \pm 0.0\text{s}$ vs. $0.3 \pm 0.0\text{s}$, $p=0.13$, $d=1.09$). Collateral ligaments constrain medio-lateral fingertip movement during MP flexion; consistent with their biomechanical property of restricting abduction as MP joint flexes (Sun et al., 2017). Wrist dorsiflexion passively flexes MP joint via finger flexor tendon tension. FLEX group likely leveraged these robust hand structural properties, reducing muscle activation cost for flexion while maintaining stability comparable to EXT. CNS strategies efficiently utilizing hand structure may simplify control, reducing muscle loading for stable movements, with implications for neurorehabilitation and robotic designs.

Disclosures: T. Ito: None. T. Kokubun: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.10/L11

Topic: F.04. Voluntary Movements

Support: NM4R - NIH P2CHD086844
Jones Movement Scholars supports Levi

Title: Targeting parietal-frontal networks to modulate hand motor function with multi-locus transcranial direct current stimulation

Authors: *T. FINKELSTEIN¹, L. KOPALD¹, L. MACMILLAN¹, B. M. HAMPSTEAD², P. J. PRUITT², T. G. LEE³, J. A. BRISSENDEN³, T. A. POLK³, S. F. TAYLOR², M. VESIA¹;
¹Sch. of Kinesiology, ²Psychiatry, ³Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Voluntary goal-directed actions - such as reaching and grasping - are mediated by multiple cortical regions in the parietal-frontal motor network rather than by isolated areas. We previously demonstrated that reduced facilitation of parietal-motor functional connections contributes to impaired skilled hand motor performance in older adults. Most transcranial direct current stimulation (tDCS) studies target a single locus - typically primary motor cortex (M1) - overlooking the posterior parietal cortex (PPC), a key hub for sensorimotor integration and skilled motor control. In addition, most prior work applies only single-session stimulation delivered at rest, often producing inconsistent and transient effects on brain and behavior. Our previous work has shown that multi-day, state-dependent theta burst stimulation of the PPC strengthens functional connectivity, induces durable plasticity, and consistently improves hand motor performance across participants. The current study tests the impact of multi-locus HD-tDCS targeting a parietal-motor circuit mediating grasp versus uni-locus HD-tDCS to M1 on hand motor function. Participants were randomized to receive either (1) network-targeted multi-locus HD-tDCS with two 4×1 montages delivering 2 mA anodal stimulation over C3 (M1) and P3 (PPC), or (2) standard uni-locus HD-tDCS with a single 2 mA anode over C3 and a cathode at Fp2. Forty healthy older adults (ages 65-85) completed three consecutive daily 10-minute HD-tDCS sessions while they performed an object-directed reach-to-grasp task. Behavioral assessments included the 9-hole peg test (9HPT) to measure manual dexterity, a force precision task evaluating fine motor control through grip force modulation, and a choice reaction time test assessing sensorimotor processing speed. Assessments were conducted before and 24 hours after the final stimulation session. Participants receiving multi-locus HD-tDCS showed improved dexterity and force precision compared to those receiving uni-locus stimulation. Future exploratory analyses will examine whether stronger simulated electric fields in parietal-frontal networks predict larger behavioral gains. These findings show that multi-day, network-targeted multi-locus HD-tDCS engages distributed motor circuits and improves hand motor performance in older adults. This work establishes a mechanistic foundation to guide the development of network-targeted stimulation protocols for enhancing motor function in older adults.

Disclosures: T. Finkelstein: None. L. Kopald: None. L. MacMillan: None. B.M. Hampstead: None. P.J. Pruitt: None. T.G. Lee: None. J.A. Brissenden: None. T.A. Polk: None. S.F. Taylor: None. M. Vesia: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.11/L12

Topic: F.04. Voluntary Movements

Support: NIH R01 AR080058

Title: Comparing single to multi-echo fMRI during a parametrically scaled grip force task

Authors: *C. E. ALEXIADIS, J. GILLIAM, F. POZZI, S. COOMBES;
Univ. of Florida, Gainesville, FL

Abstract: Understanding how the human brain scales force production is a foundational principle of motor neuroscience. Functional magnetic resonance imaging (fMRI) is an excellent tool to study brain function during force control, but studying the active motor system during fMRI is challenging due to noise and task-correlated head motion. Current knowledge of how the human brain scales force production comes from conventional motor fMRI studies that have implemented single echo (SE-fMRI) pulse sequences. Although multi-echo fMRI (ME-fMRI) studies have shown that collecting multiple TEs per pulse can decrease signal loss and reduce motion artifacts, it is not clear whether a ME-fMRI sequence enhances the ability to differentiate BOLD signal between different force levels. We collected ME-fMRI from young, healthy adults during a visually guided pinch grip motor task at two force levels (15% and 30% maximum voluntary contraction). Our goal was to directly compare the BOLD signal between force levels when using a SE-fMRI sequence (TE = 33.43) compared to a ME-fMRI sequence (TEs: 9.02/33.43/57.84). Data were processed using *tedana* in AFNI which optimally combines echoes and then performs independent component analysis to further separate BOLD and non-BOLD components. We report three findings. First, greater activation was found in the visuomotor network (including M1, PMd, IPL, V5) for the high>low force contrast when using ME-fMRI compared to SE-fMRI. This suggests that the ME-fMRI has increased sensitivity to detecting differences in the amplitude of force production. Second, we confirmed that the signal to noise ratio was significantly higher in ME-fMRI data compared to SE-fMRI. Third, framewise displacement (DVARS) of the head was similar in both processing methods; however, DVARS was lower in ME-fMRI scans, indicating that the ME-fMRI approach was more effective in identifying and removing sudden changes in the BOLD signal than the SE-fMRI approach. These results confirm previous findings that ME-fMRI enables more effective identification and removal of noise due to motion artifacts. Together our observations demonstrate that identifying and removing artifacts using ME-fMRI increases sensitivity to changes in the BOLD signal in the visuomotor network as the brain scales force output.

Disclosures: C.E. Alexiadis: None. J. Gilliam: None. F. Pozzi: None. S. Coombes: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.12/L13

Topic: F.04. Voluntary Movements

Support: NIH R21
NSF CRCNS US-Japan
the Wu Tsai Human Performance Alliance at Stanford University

Title: The importance of muscle coordination in generating natural “cascading” of the fingers: Implementation in a biorobotic finger

Authors: *N. J. S. MATHARU¹, F. J. VALERO-CUEVAS², K. WANKHEDE³;
¹Alfred E. Mann Dept. of Biomed. Engin., ²Biomed. Engin., ³USC, Los Angeles, CA

Abstract: Objective: To investigate the role neuromuscular coordination plays in generating the equiangular spiral observed in human fingers.

Restoring the coordinated flexion of the joints of the human fingers (i.e., cascading, Littler, 1973) is critical to tendon transfers in spinal cord injury and neurorehabilitation in stroke and other neurological conditions. This coordinated movement approximates an equiangular spiral trajectory, in which the interphalangeal joint angles are equal during flexion. This pattern has been observed and described in both clinical and kinematic studies and is thought to underlie the hands' ability to delicately and precisely manipulate objects (Littler, 1973; Gupta et al., 1998; Kamper et al., 2003). Therefore, it is critical to quality of life. Current robotic analogs of human fingers aim to reproduce the equiangular spiral through the mechanical properties of the system (Wang, Freris, and Wei, 2025), and implementation of kinematic coupling as per the extensor mechanisms and Landsmeer ligament (Hentz & Leclercq, 2002). However, human fingers do not follow the spiral perfectly with every grasp, and the movement is easily disrupted in neurological conditions and partial paralysis, demonstrating that muscle coordination is crucial (Kamper, et al., 2003; Valero-Cuevas & Hentz, 2002). We aim to investigate the role of neuromuscular mechanisms in generating this characteristic pattern in a semi-soft biorobotic finger.

We developed a 12cm tendon-driven, semi-soft finger with 4 cm link lengths. These rigid links were encapsulated in silicone to mimic a human finger, hence ‘semi-soft.’ Tendons were routed per the N+1 design (Valero-Cuevas, 2016), a strategy where N represents the degrees of freedom (here, two). Tendons are routed to cross and thus actuate multiple joints simultaneously. We define the equiangular spiral as a movement such that the flexion angles at interphalangeal joints are equal ($\angle J1 = \angle J2$). We use a Reinforcement Learning (RL) algorithm to find sequences of tendon activation sets that lead to the finger approximating an equiangular spiral as we defined. Our null hypothesis (H0) posits that no such tendon activation pattern exists — supporting the emphasis on the mechanical design of human fingers to replicate this motion. The alternative

hypothesis (H1) proposes that at least one pattern approximates the equiangular spiral. We anticipate that our RL algorithm will identify a narrow, brittle, path of optimal neuromuscular control capable of generating the characteristic equiangular spiral—thus explaining its common clinical emergence.

Disclosures: N.J.S. Matharu: None. F.J. Valero-Cuevas: None. K. Wankhede: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.13/L14

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI, JP22K17628

Title: Effects of Repetitive Peripheral Magnetic Stimulation on Spinal Reciprocal Inhibition in Healthy Individuals

Authors: *D. MIYAZAKI¹, M. NITO²;

¹Grad. Sch. of Hlth. Sciences, Yamagata Prefectural Univ. of Hlth. Sci., Yamagata, Japan;

²Occup. Therapy, Yamagata Prefectural Univ. of Hlth. Sci., Yamagata, Japan

Abstract: Repetitive peripheral magnetic stimulation (rPMS) has been reported to improve motor dysfunction and spasticity following central nervous system disorders. However, its underlying neural mechanisms remain poorly understood. This study aimed to investigate the effects of rPMS on reciprocal Ia inhibition (RI) and D1 inhibition between the wrist flexor and extensor muscles in thirty healthy adults. rPMS was applied to the extensor carpi radialis (ECR) in a 2-s ON and 2-s OFF cycle for a total duration of 15 min. First, the effects of rPMS on RI and D1 inhibition directed from ECR to the flexor carpi radialis (FCR) were assessed before, 5 min, 10 min, 15 min, and 20 min after rPMS. RI and D1 inhibition were evaluated as the inhibition of the FCR H-reflex following radial nerve stimulation with interstimulus intervals of -5 to 0 ms and 13 ms, respectively. rPMS at an intensity sufficient to elicit muscle contraction significantly enhanced RI, whereas no significant modulation was observed following rPMS at an intensity that did not elicit muscle contraction. No significant changes in D1 inhibition were observed with either intensity of rPMS. Next, the effects of rPMS on RI and D1 inhibition directed from FCR to ECR were assessed at the same time points. RI and D1 inhibition were evaluated as the inhibition of the ECR H-reflex (or tendon jerk) following median nerve stimulation at interstimulus intervals of 1 to 3 ms (-8 to -2 ms in tendon jerk) and 20 ms, respectively. rPMS at an intensity that elicited muscle contraction significantly reduced RI, whereas no significant changes in D1 inhibition were observed. Moreover, unconditioned H-reflex (or tendon jerk) amplitudes remained stable. Our results revealed that rPMS applied to the wrist extensors enhanced RI from the stimulated muscles to antagonist motoneurons, whereas RI in the opposite

direction was attenuated, suggesting that rPMS modulates reciprocal inhibition in a direction-dependent manner.

Disclosures: D. Miyazaki: None. M. Nito: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.14/L15

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI 22K17628
31th Magnetic Research Grant from Watanabe Foundation

Title: Contribution of Group Ia Afferents to Enhancement of Corticospinal Excitability by High-Intensity Repetitive Peripheral Magnetic Stimulation

Authors: *M. NITO^{1,2}, K. YOSHIDA², T. YAMAGUCHI³;

¹Occup. Therapy, Yamagata Prefectural Univ. of Hlth. Sci., Yamagata, Japan; ²Grad. Sch. of Hlth. Sciences, Yamagata Prefectural Univ. of Hlth. Sci., Yamagata, Japan; ³Physical Therapy, Grad. Sch. of Medicine, Kyoto Univ., Sakyo-ku, Kyoto, Japan

Abstract: Repetitive peripheral magnetic stimulation (PMS) has been applied in clinical settings to enhance the recovery of motor function following central nervous system lesions. However, the optimal intensity of PMS for inducing neural plasticity and the mechanisms behind its action are poorly understood. Here, we investigated the effects of different intensities of PMS on corticospinal excitability and single motor unit firings. Participants underwent PMS at 25 Hz, administered to the extensor carpi radialis (ECR) muscle in a 2-s ON, 2-s OFF cycle. Stimulation was delivered at three stimulus intensity levels: just below the motor threshold ($0.9 \times MT$), above the motor threshold ($1.2 \times MT$), and at a high intensity sufficient to elicit maximal wrist dorsiflexion (mean $\pm$ SD: $1.8 \pm 0.3 \times MT$). The PMS consisted of five sessions for a total of 15 min (3 min per session), and motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation were measured before (T0), between (T3, T6, T9, T12), and after sessions (T15). A significant increase in ECR MEPs was observed at T9, T12, and T15 in high-intensity PMS, as well as at T15 in PMS at $1.2 \times MT$. In contrast, no significant changes were detected following $0.9 \times MT$ of PMS. Furthermore, across all PMS intensities examined, no significant change in MEPs of the flexor carpi radialis was observed. Next, to investigate the lasting effects of 9 min high-intensity PMS, MEPs were measured 5 min before (baseline), just before (Pre), and every 10 min for 50 min after PMS (Post 0, 10, 20, 30, 40, and 50). A significant increase in ECR MEPs was observed following PMS for up to 30 min. However, PMS applied after ischemia at the arm, which diminished the ECR H-reflex, failed to induce ECR MEP augmentation, suggesting that Ia afferents originating from muscle spindles contribute to MEP augmentation by PMS. Further, to compare the estimated magnitude of sensory input elicited by three intensity

levels of PMS, we investigated the effects of PMS on single motor unit firings in the ECR. Post-stimulus time histograms were constructed following PMS. An early and significant peak (an increase in the firing probability) was observed following PMS. The peak size was more pronounced with high-intensity PMS and PMS at 1.2xMT, but PMS at 0.9 x MT did not induce such a peak, suggesting that subthreshold PMS is insufficient to activate afferent input. Taken together, PMS at intensities above the motor threshold enhances corticospinal excitability via activation of group Ia afferents.

Disclosures: M. Nito: None. K. Yoshida: None. T. Yamaguchi: None.

Poster

PSTR026: Finger and Grasp Control: Human Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR026.15/M1

Topic: F.04. Voluntary Movements

Support: EKÖP-EFOK-9-2024
JSPS KAKENHI 21K17600

Title: Neural mechanisms behind the interaction between handedness and the complexity of the motor sequence task

Authors: *J. NEGYESI^{1,2,3}, J. ZHAO⁴, Y. WANG⁴, G. BOLLA², M. BECSKE², D. SZIRMAI², A. HORVATH², S. SHIOIRI⁵, R. NAGATOMI⁵;

¹Hungarian Univ. of Sports Sci., Budapest, Hungary; ²Nyíró Gyula Natl. Inst. of Psychiatry, and Addictology, Neurocognitive Res. Ctr., Budapest, Hungary; ³CRU Hungary Ltd., Budapest, Hungary; ⁴Jilin Med. Univ., Jilin City, China; ⁵Tohoku Univ., Sendai, Japan

Abstract: Introduction: Accuracy and the time required to react and perform a motor task differ when the dominant versus non-dominant hand is used, due to the functional laterality of the human brain. A wealth of literature suggests that such laterality interacts with sequence complexity; however, it remains unclear whether handedness influences this interaction. The objective of the present study was to investigate the neural correlates of the interaction between laterality and sequence complexity concerning handedness. **Methods:** Strongly left- (n = 15, age = 24.9 ± 3.3 years) and right-handed (n = 15, age = 26.4 ± 4.4 years) participants performed finger key presses on a numeric keypad at four levels of sequence complexities with each hand in a randomized order. The experiment was conducted in a dimly lit and electromagnetically shielded room, using a 19-inch. (37.7 × 30.1 cm screen size) IBM LCD display (1280 × 1024 screen resolution). The stimuli were presented using custom-made software. In addition to behavioural data (accuracy, reaction time, movement time, mental workload [NASA-TLX]), brain activity was monitored with a high-density electroencephalogram (EEG, BioSemi, Netherlands) at a sampling rate of 2048 Hz. The EEG data were processed using EEGLAB, an open-source toolbox running in the MATLAB2021b environment. **Results:** In line with our

previous findings, 1) both right-handed ($p = 0.033$, $d = -0.295$) and left-handed ($p = 0.027$, $d = 0.311$) participants performed the motor sequence task with faster RT when using their right hand, and 2) they tended to increase RT and MT with increasing sequence complexity (all $p < 0.05$); nevertheless, these associations were unrelated to sequence complexity and handedness, respectively. Moreover, there were main effects of sequence complexity in selected EEG power bands; however, the only correlations found were between contralateral theta band activity and RT ($\rho_{\text{os}} = 0.324$, $p = 0.011$) and MT ($\rho_{\text{os}} = 0.312$, $p = 0.015$) at level 4. **Conclusions:** Overall, our results suggest that neural representations for an increased reaction time and movement time appear only in the contralateral hemisphere when the motor sequence task is the most complex, regardless of handedness and the performing hand.

Disclosures: J. Negyesi: None. J. Zhao: None. Y. wang: None. G. Bolla: None. M. Becske: None. D. Szirmai: None. A. Horvath: None. S. Shioiri: None. R. Nagatomi: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.01/M2

Topic: F.04. Voluntary Movements

Support: Swiss National Science Foundation (Grant Number 32003B_208110)

Title: Reticulospinal involvement in the control of multi-joint movements requiring endpoint accuracy

Authors: *L. C. NEUMANN^{1,2}, A. VAN DEN BROEK³, L. FILLI^{3,2,4};

¹Spinal Cord Injury Ctr., Balgrist Univ. Hospital, Univ. & ETH Zurich, Zürich, Switzerland;

²Neurosci. Ctr. Zurich, Univ. and ETH Zurich, Zurich, Switzerland; ³Spinal Cord Injury Ctr., Balgrist Univ. Hospital, Univ. of Zurich, Zurich, Switzerland; ⁴Swiss Ctr. for Movement Analysis, Zurich, Switzerland

Abstract: The reticulospinal system (RS) is a key pathway involved in movement control, particularly for synergized multi-muscle actions like reaching movements. The StartReact effect, which utilizes a loud acoustic stimulus (LAS) to trigger movements subcortically, has provided insights into RS motor control in humans. While StartReact effects are well-documented in simple single-joint tasks, the role of the RS system in more complex, multi-joint movements requiring endpoint accuracy remains vaguely understood. This study aims to assess RS motor control in pointing movements requiring endpoint accuracy.

To date, 7 of 19 planned healthy participants (5 female, 24.1 ± 6.6 years) performed a StartReact paradigm where they were instructed to point as fast as possible to one of three physical targets presented in front of them after hearing the imperative stimulus (i.e., either moderate (MAS; 85 dB) or loud acoustic stimuli (120 dB). Reaction times were assessed using surface

electromyography from 6 muscles, and movement kinematics were recorded via motion capture. Reaction times were significantly shorter in LAS trials compared to control trials for both the anterior deltoid and biceps brachii, confirming the StartReact effect. Sagittal movement trajectories showed greater initial vertical displacement and higher vertical endpoint overshoot for LAS trials. LAS trials showed greater errors in target accuracy than control trials. The findings confirm the presence of the StartReact effect in multi-joint reaching movements. The observed differences in movement kinematics suggest that reticulospinal inputs predominantly influence early aspects of the movement, while later movement phases may also be controlled by corticospinal commands. The reduced endpoint accuracy in LAS trials indicates that, although corticospinal commands likely contribute to the pointing accuracy in both conditions, these inputs are less dominant in LAS than MAS trials, aligning with Fitts' law. The findings of this study suggest RS contributions to complex, targeted multi-joint reaching movements, particularly during the early ballistic phase of the movement. Differences in target accuracy indicate a changed pattern of interaction between the RS and corticospinal system in mediating the pointing task. These findings provide insights into the complex interaction of the main descending motor tracts during multi-joint movements.

Disclosures: L.C. Neumann: None. A. van den Broek: None. L. Filli: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.02/M3

Topic: F.04. Voluntary Movements

Support: NIH

Title: Functional Role of Excitatory Neurons in the Pontine Reticular Nuclei in Locomotor Control

Authors: *M. B. SEO¹, G. ZHANG², J. J. HUANG³, W. SUN⁴, K. SU¹, H. W. TAO⁵, L. I. ZHANG¹;

²Dept. of Neurosci. and Physiol., ¹USC, Los Angeles, CA; ³Zilkha Neurogenetic Inst., USC, LOS ANGELES, CA; ⁴Zilkha Neurogenetic Inst., USC, Los Angeles, CA; ⁵Physiol. and Neurosci., USC Keck Sch. Med., Los Angeles, CA

Abstract: The brainstem acts as a key relay between upper motor centers and the spinal cord, coordinating various aspects of locomotor behavior. Recent studies have identified modular circuits within the brainstem that command specific actions such as forward locomotion, turning, and forelimb movements. However, whether distinct subpopulations execute additional behaviors remains unclear. In this study, we combine c-Fos, in vivo calcium imaging, bidirectional optogenetic manipulation, and viral circuit tracing to investigate the functional role

and anatomy of excitatory neurons within the pons. Our results identify a previously unrecognized brainstem node essential for locomotor control, providing new insights into the modular organization of motor commands.

Disclosures: M.B. Seo: None. G. Zhang: None. J.J. Huang: None. W. Sun: None. K. Su: None. H.W. Tao: None. L.I. Zhang: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.03/M4

Topic: F.04. Voluntary Movements

Title: Muscles Do Not Primarily Generate Force

Authors: *F. TESSARI, N. HOGAN;
MIT, Cambridge, MA

Abstract: Humans present a remarkable ability to handle physical interaction despite a tremendously complex musculoskeletal system, comparatively slow muscles and slow neural communication. Most physical interaction tasks require force generation which can - in some cases - compromise stability. For example, pushing on a screwdriver or performing a bench press exercise require both force and stabilization. In order to ensure stability, muscles are required to produce a certain mechanical impedance (especially stiffness and damping). In this work we investigate the human limits of force generation and test whether and how those limits are constrained by our ability to stabilize the task. Moreover, we also study how strongly limb configuration - which is known to play a key role in transmitting muscle tension to hand force - matters in the generation of force. To probe these research questions, we devised an experiment in which healthy individuals were required to perform a maximum voluntary pushing task using a custom designed gimbal apparatus which allowed us to conditionally change the degrees of freedom of the wrist, thus enabling or disabling stabilization via wrist pronation-supination, ulnar-radial deviation, and flexion-extension. The experiment was repeated in two different arm configurations (subject-preferred and constrained to maximum pronation) to assess the effect of arm configuration. The results showed: (i) a statistically significant and substantial decrease in maximum output force by disabling more wrist degree of freedom, and (ii) a significant but less-than noticeable difference in maximum pushing force between the two arm configurations. Interestingly, subjects unexpectedly improved their maximum pushing performance between pre- and post experiment, thus suggesting a negligible effect of fatigue and a possible effect of learning. Our findings confirm our hypothesis that force is limited by the ability to stabilize an unstable physical interaction, and thus that muscles do not primarily generate force, but simultaneously also generate impedance, specifically stiffness in this case. Furthermore, the fact that diverse arm configurations could generate less-than noticeable differences in maximum

pushing force emphasize the versatility of our musculoskeletal system and the possibility to find multiple solution for the same motor tasks, in agreement with the Synergy Expansion hypothesis.

Disclosures: F. Tessari: None. N. Hogan: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.04/M5

Topic: F.04. Voluntary Movements

Support: 1R01NS134754-01A1

Title: Observation Alone Does Not Drive Speech Adaptation: Supporting a Role for Motor Planning

Authors: B. PARRELL¹, *M. BAE¹, C. NABER¹, O. A. KIM², C. A. NIZIOLEK¹, S. D. MCDOUGLE³;

¹Univ. of Wisconsin–Madison, Madison, WI; ²Bates Col., Lewiston, ME; ³Yale Univ., New Haven, CT

Abstract: We adjust our movements by comparing sensory predictions with sensory feedback and updating an internal model to reduce discrepancies. Previously, we found that reach adaptation can occur when a movement is planned but not executed, suggesting motor planning is sufficient to drive adaptation (Kim et al., 2022, PNAS). We recently replicated this effect in speech (Parrell et al., 2025, bioRxiv). However, it is currently unclear whether this result can be solely attributed to motor planning, or whether alternative mechanisms, such as observational learning (Mattar and Gribble, 2005, Neuron), may have contributed. To test this, we examined whether speech adaptation occurs under observation of errors when motor planning is not involved.

Speakers (N = 17; 15 female; age = 21.5 ± 7.5) were prompted to speak a visually presented word. In movement trials, a "speak" cue appeared before the stimulus indicating participants should read the word aloud, while hearing either perturbed (± 125 mels shift to F1) or unperturbed auditory feedback. In observation trials, a "don't speak" cue indicated participants should remain silent, while passively listening to a perturbed recording from the prior trial. Trials were organized into three-trial triplets, where the middle trial (either movement or observation) received perturbed feedback, while the first and third trials (always movement trials) did not. Single-trial adaptation was measured as the F1 change between the first and third trials, and aftereffects by comparing the first trial to the following trial. Based on previous work, these were combined to improve statistical power.

Adaptation occurred only in movement trials: in movement trials, F1 was higher after downward shifts (-1.39 ± 1.11 mels) than after upward ones (-6.38 ± 1.11 mels; $t(6511) = 3.29$, $p = .001$),

with no difference in observation trials (down: -0.77 ± 0.87 mels, up: -1.20 ± 0.84 mels; $t(6501) = 0.37$, $p = .710$; LME direction $\times$ condition $F(1, 6526) = 5.80$, $p = 0.016$). Separate analyses of single-trial adaptation and retention showed a similar pattern: adaptation only occurred in movement trials (adaptation: $t(3255) = 2.69$, $p = .007$; retention: $t(3237) = 1.99$, $p = .047$), and not observation trials (both $p > .5$). Direction $\times$ condition interactions were significant for adaptation ($F(1, 3265) = 4.49$, $p = .03$), but not for retention ($F(1, 3252) = 1.69$, $p = .19$). These findings strongly suggest that previously-observed adaptation in the absence of movement execution was not driven by observational learning, and support the conclusion that, across motor domains, sensorimotor adaptation is supported by sensory predictions generated during motor planning.

Disclosures: M. Bae: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.05/M6

Topic: F.04. Voluntary Movements

Support: NIH Grant 5T32NS007431-23
NIH Grant 5T32NS007431-24
1R01NS118030-01A1

Title: Integration of motor commands in the pontine nuclei

Authors: *R. B. SHUGG¹, A. J. KHALIL², V. MENON³, S. SPIJKER², H. D. MANSVELDER², J. D. COHEN¹, L. WITTER⁴, A. W. HANTMAN¹;

¹Neurosci. Ctr., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; ²Dept. of Integrative Neurophysiology, Ctr. for Neurogenomics and Cognitive Res., Vrije Univ. Amsterdam, Amsterdam, Netherlands; ³Dept. of Neurol., Columbia Univ., New York, NY; ⁴Dept. for Developmental Origins of Disease, UMC Utrecht Brain Ctr., Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Skilled movements require real-time adaptations to flexibly respond to the environment, a function often attributed to the cerebellum. Since the cerebellum predominantly receives cortical input from the pontine nuclei (PN), understanding the role and computations of the PN is essential to build a complete model of the motor circuit. Yet, the role of the pontine nuclei in the motor circuit remains unclear. The pontine nuclei is organized topographically with axons from distinct cortical regions projecting to specific terminal zones. We have identified widely branching pontine neurons, with dendrites surpassing the length of cortical terminal zones, implying convergence and integration of cortical information in the pontine. We therefore tested how pontine neurons integrate cortical signals.

We trained mice to perform a dexterous reach-to-grab task wherein naive mice were trained to reach for a food pellet upon presentation of an auditory cue. Mice achieved high performance on this task within two to three weeks of daily training. Next, we performed largescale electrophysiology recordings in the pontine nuclei during the reach-to-grab task. Additionally, in the same recordings, we conducted both single and dual optic fiber optogenetic stimulation experiments over the somatomotor cortex in VGLUT1/Ai32 mice to test whether pontine neurons receive convergent input and/or integrate cortical inputs.

Neuron stimulation responses met selection criteria to be included in the analysis, including the peak latency to spike from onset of stimulation, the probability of spiking, and the trial-to-trial spike timing consistency. We found that a subgroup of neurons in the pontine nuclei receive convergent inputs from more than one stimulation location. Additionally, neurons that receive a greater number of convergent inputs are more likely to be functionally modulated during skilled movement. Furthermore, neurons have a variety of linear and nonlinear responses to dual fiber stimulations, suggesting a complex and diverse computational role of neurons in the pontine. These results support the hypothesis that there is a subset of neurons in the pontine that converge and integrate cortical inputs, which also aligns with our morphological and electrophysiological evidence for convergence and integration.

Disclosures: R.B. Shugg: None. A.J. Khalil: None. J.D. Cohen: None. L. Witter: None. A.W. Hantman: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.06/M7

Topic: F.04. Voluntary Movements

Title: Mental chronometry of memory-guided sequence production

Authors: *M. G. POTTA¹, C. CARACCIO², M. JAZAYERI³;

¹Electrical Engin. and Computer Sci., MIT, Cambridge, MA; ²Hlth. Sci. and Technol., Harvard-MIT, Cambridge, MA; ³Brain and Cognitive Sci., Massachusetts Inst. of Technol. Dept. of Brain and Cognitive Sci., Cambridge, MA

Abstract: A key feature of memory-guided sequence production is the consistent increase in reaction times (RT) as sequence length grows (Sternberg et al., 1978; Klapp, 1995). This increase is evident even after delays long enough to allow subjects to prepare their responses (Maslovat et al., 2019; Khan et al., 2024). Furthermore, this pattern disappears only after moderate to extensive practice, requiring more than 300 repetitions (Verwey, 1999). This robust chronometric signature is observed not only in humans but also across the animal kingdom, including species ranging from macaques (Swartz et al., 1991) and chimpanzees (Ohshiba, 1997) to crows (Liao et al., 2024). Why does it take longer to respond to longer sequences, and why

does this delay occur even in the presence of a highly predictable stimulus? Does it reflect the data structure underlying the motor planning buffer? Is it a result of serial communication between memory areas and the motor system? Or could it relate to the episodic nature of the information? In other words, is the bottleneck with the destination, the transmission, or the storage? We think this phenomenon reflects a core computational principle by which biological systems organize and generate sequential actions from memory—one that current models do not capture. To address these questions, we developed a computerized version of the classic Simon, a memory game with four colored buttons. In each round, the game lights up a sequence of colored buttons in a fixed temporal order, and the player must repeat the sequence by pressing the same colored buttons in order. The sequence starts with one color and grows by one color each round. When the player makes a mistake, the game resets and a new sequence is initiated. Participants' RTs featured the expected scaling effect robustly for novel sequences and even beyond the previously reported eight-element limit. Moreover, RT scaling was systematically modulated by sequence complexity, internal repetition structure, and externally imposed response-time constraints. Our ongoing work aims to leverage this experimental platform to combine behavior, electroencephalography (EEG), and biologically-inspired neural network modeling to rigorously test mechanistic hypotheses regarding the neurobiological mechanisms of memory-guided sequence production. Specifically, we will use the chronometric behavioral signatures and event-related potentials (ERPs) that reflect actively maintained representations in visual working memory (Vogel & Machizawa, 2004) to develop models that can capture how humans encode, maintain, and retrieve sequential information under varying cognitive loads.

Disclosures: M.G. Potta: None. C. Caraccio: None. M. Jazayeri: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.07/M8

Topic: F.04. Voluntary Movements

Support: Multidisciplinary Frontier Brain and Neuroscience Discoveries
(Brain/MINDS 2.0) JP24wm0625315

Title: Chemogenetic activation of convergent spinal pathways improves sensorimotor performance of forelimb in nonhuman primates

Authors: *M. SUZUKI¹, O. YOKOYAMA², K. KOBAYASHI³, S. I. PERLMUTTER⁴, Y. NISHIMURA²;

¹Tokyo Metro Inst. Med. Sci., Tokyo, Japan; ²Neural Prosthetics Project, Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan; ³Natl. Inst. For Physiological Sci., Okazaki, Japan; ⁴Dept Neurobio. & Biophysics, Washington Natl. Primate Res. Ctr., Univ. of Washington, Seattle, WA

Abstract: Ablation of descending motor and somatosensory afferent inputs to the spinal cord impairs sensorimotor functions, highlighting their essential role in voluntary movement. While their physiological contribution is well established, it remains unclear whether exogenous enhancement of these pathways can influence behavior. Here, we use designer receptors exclusively activated by designer drugs (DREADDs) to demonstrate a causal relationship between increased neuronal activity of convergent inputs to the cervical enlargement and sensorimotor behavior in nonhuman primates. A retrograde viral vector encoding the excitatory DREADD hM3Dq was unilaterally injected into the cervical enlargement. Administration of a DREADD-selective agonist under anesthesia increased spontaneous activity in the sensorimotor cortices and forelimb muscle activity in a dose-dependent manner, and also elevated the gain of the spinal stretch reflex. Furthermore, in behaving monkeys, chemogenetic activation increased arm-reaching speed, grip force velocity, and sensitivity to nociceptive heat stimulation. To examine whether this activation can compensate for cortical dysfunction, we transiently inactivated the hand regions of the primary motor cortex (M1) and primary somatosensory cortex (S1) via local muscimol injection. Inactivation of M1 and/or S1 impaired sensorimotor performance, as demonstrated by slower reaching and grip movements, reduced finger dexterity, and diminished sensitivity to nociceptive heat stimulation. Under these conditions, chemogenetic activation improved reaching speed and grip force velocity, suggesting partial recovery of gross motor function. Although finger movements were facilitated, finger dexterity was not immediately restored. Additionally, responses to nociceptive heat stimuli were similar to those observed with vehicle treatment, indicating no specific effect attributable to chemogenetic activation. In conclusion, chemogenetic enhancement of convergent spinal inputs modulates sensorimotor behavior and acutely compensates for motor deficits induced by cortical inactivation, suggesting a potential therapeutic strategy for restoring motor function after central nervous system damage.

Disclosures: M. Suzuki: None. O. Yokoyama: None. K. Kobayashi: None. S.I. Perlmutter: None. Y. Nishimura: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.08/M9

Topic: F.04. Voluntary Movements

Support: Else Kröner Fresenius Center for Optogenetic Therapies (EKFZ)

Title: A markerless tracking setup for examining a large variety of grasping movements in macaque monkeys

Authors: *N. ZDUN^{1,2}, H. SCHERBERGER^{1,2}, B. DANN¹;

¹German Primate Ctr., Göttingen, Germany; ²Georg-August-Universität, Göttingen, Germany

Abstract: Understanding the neural mechanisms underlying movement generation is a fundamental goal in systems neuroscience. Grasping, a critical function for interacting with the environment, involves a diverse range of complex hand movements. However, most studies have only explored a limited subset of grasp types, raising concerns that significant movement dynamics may remain undiscovered. Previous research has demonstrated that neural activity during grasping can be explained by a small number of latent dimensions, suggesting low-dimensional representations of motor control. Yet, it remains unclear whether this low dimensionality is an artifact of constrained experimental designs or a fundamental principle of brain dynamics. To address this question, we have developed a novel experimental setup that enables the recording and classification of an unprecedented number of grasping movements in non-human primates. Our setup utilizes a conveyor belt system to present a diverse set of objects in randomized order, ensuring a broad exploration of grasp types. Objects can be exchanged between trials and rotated into different orientations to maximize variability. To capture the full kinematic complexity of grasping, we employ a markerless tracking method (Jarvis software package), which enables precise motion tracking via multiple video cameras without interfering with behavior. The recorded kinematic data is analyzed using Uniform Manifold Approximation and Projection (UMAP) and Louvain clustering to categorize different grasping poses. This approach allows for a detailed classification of hand movements and provides insights into the diversity of grasping strategies. By leveraging this high-resolution dataset, we aim to create a comprehensive taxonomy of grasp types and investigate how grasping behavior adapts to varying object properties and orientations.

Disclosures: N. Zdun: None. H. Scherberger: None. B. Dann: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.09/M10

Topic: F.04. Voluntary Movements

Support: NIH Grant F99 NS141305
NSF EFRI-BRAID 22223822,
NIH R01DC018446
NIH R01DC018055

Title: Latent premotor neural dynamics reveal species-specific vocalization strategies in songbirds

Authors: *J. C. GORMAN¹, E. M. ARNEODO³, L. OSTROWSKI⁴, P. TOSTADO MARCOS², T. MCPHERSON⁵, L. STANWICKS⁶, T. Q. GENTNER⁷;

¹UC San Diego, La Jolla, CA; ²Bioengineering, UC San Diego, San Diego, CA; ³Psychology, Univ. of California San Diego, La Jolla, CA; ⁵Neurosci., ⁴UCSD Dept. of Neurosciences, La

Jolla, CA; ⁶Psychology - McGill Hall, Univ. Of California San Diego, SAN DIEGO, CA;
⁷Psychology, Univ. Of California San Diego Neurosciences Grad. Program, La Jolla, CA

Abstract: Vocal flexibility is a hallmark of human language, but how this flexibility emerges from the dynamics of neural population activity remains unknown. Singing in oscine birds offers a powerful model for studying the neural control of learned vocal behavior using well-characterized neural circuits and natural behaviors with varying flexibility. Despite similar neuroanatomy, song flexibility varies greatly over the ~4500 species of songbirds, with some species producing highly stereotyped songs and others more degenerate vocal sequences. To investigate how neural dynamics and control strategies relate to vocal flexibility, we recorded neural population activity from the sensory-motor region HVC during singing in two species: zebra finches (ZF; *Taeniopygia guttata*), which sing stereotyped songs with ordered motifs, and European starlings (EST; *Sturnus vulgaris*), which produce more variable sequences and modify songs throughout life. We compared latent trajectories defined by covariant HVC activity during singing. In ZF, trajectories during song motifs (n=23 bouts) were low-dimensional and internally consistent, with >85% of variance captured by two latent dimensions. Overall, trajectories for repeated motifs were highly similar but not uniform across time. Silence immediately preceding motifs showed highest similarity, indicating structured dynamics at vocal onset, while ends of motifs and intra-syllable notes were more variable. In contrast, in EST, whose songs lack stereotyped motifs, latent trajectories were higher-dimensional and more spatially diffuse. EST HVC population activity evolves continuously during singing without returning to fixed points or repeating trajectories, and the first two latent dimensions capture much less (<60%) of neural response variance (n=32 song bouts). EST trajectories show minimal cyclicity compared to ZF, yet dynamics during similar syllables remain highly similar even when sung at different times. Our findings support a continuum of control strategies in HVC across species. In ZF, neural trajectories are low-dimensional and consistent during stereotyped song segments with structured attractor-like dynamics. In EST, increased vocal complexity is tied to higher dimensional and more variable HVC neurodynamics throughout the song, that can still be tied in local regions of the neural subspace to song acoustics. Species-specific differences in the temporal dynamics of HVC likely reflect differences in how and when internal and/or external variables drive neurodynamical state transitions, with the latter hypothesized to come in the form of external sensory-driven feedback error.

Disclosures: J.C. Gorman: None. E.M. Arneodo: None. L. Ostrowski: None. P. Tostado Marcos: None. T. McPherson: None. L. Stanwicks: None. T.Q. Gentner: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.10/M11

Topic: F.04. Voluntary Movements

Support: APDA 1053521
NIH (NINDS) T32 NS115724

Title: Significant Delta-Beta Phase Amplitude Coupling Between the Motor Thalamus and Cortex Prior to the Initiation of Movement

Authors: *G. PAIER, E. BENCE, C. E. LEE, E. OPRI;
Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Deep brain stimulation (DBS) is an established treatment for individuals with movement disorders. Understanding the neural activity underlying movement is necessary to improve spatiotemporal efficacy of DBS. Delta and beta oscillations play distinct roles in motor control, and cross-frequency interactions between these bands have emerged as critical markers of motor readiness and volitional movement. Specifically, prior work has shown significant delta-beta phase amplitude coupling (PAC) in the ventral intermediate nucleus (VIM) of the thalamus prior to the initiation of cued movement, suggesting the role of delta oscillations in the VIM in modulating motor related beta activity (Gaidica et al. 2020). Additionally, significant delta-beta PAC in human primary motor cortex (M1) may reflect task related attentiveness and motor readiness (Saleh et al. 2010).

However, the role of delta-beta VIM-M1 PAC between these structures in motor control has not been well established in humans. Opri et al. 2019 showed significant PAC between low-frequency oscillations in VIM and high frequency oscillations in the motor cortex (M1) prior to movement, showing thalamic regulation of cortical excitability. We used this dataset to determine the relationship delta-beta PAC between the motor thalamus and cortex with respect to the initiation of movement. Essential tremor patients were visually cued to pretend to drink from and cup using either their left or right hand. The Tort method was used to define PAC as a measure of nonuniformity in amplitude distribution across phase (Tort et al. 2010). Statistical significance is computed leveraging a surrogate analysis by randomly time-shifting phase estimates. For within-node PAC, delta-beta PAC was significant within M1 during the movement period ($p < 0.05$) and within VIM during the preparatory period ($p < 0.05$). Interestingly, VIM delta and M1 beta showed significant PAC in the preparatory period ($p < 0.05$), but not during baseline, rest, and movement periods. Furthermore, the preferred VIM delta phase for significant coupling to M1 beta amplitude prior to the initiation of movement was the rising phase of delta (0 radians).

Such coupling would suggest movement intention in response to a visual cue extends beyond the cortex, involving thalamic regulation of motor cortical neurons. This understanding is crucial to the foundational knowledge of kinematic control by characterizing neural signaling that promotes movement in humans. This finding provides further avenues for a control marker for adaptive stimulation paradigms that aim to promote prokinetic signaling in treatments for individuals with movement disorders.

Disclosures: G. Paier: None. E. Bence: None. C.E. Lee: None. E. Opri: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.11/M12

Topic: F.04. Voluntary Movements

Title: Amplitude and latency changes in readiness potential and event-related synchronization/desynchronization during voluntary movements with modulated time duration

Authors: *A. AVALOS SALGADO^{1,2}, H. GALVAN GUERRERO², V. RAMOS SCALABRIN², O. BECERRA CASILLAS², L. P. OSUNA CARRASCO², M. TREVINO VILLEGAS³, B. DE LA TORRE²;

¹Univ. de Guadalajara, Zapopan, Mexico; ²Bioingenieria Traslacional, Univ. de Guadalajara, Guadalajara, Mexico; ³Mind/Brain Inst., Inst. De Neurociencias Udeg, Guadalajara, Mexico

Abstract: The readiness potential (RP) and event-related synchronization / desynchronization (ERS/ERD) are EEG figures which are timelocked to a conscious movement, this time marker has slight variations in between experimental subjects. The RP is present from 2 s before movement up to 0.5 s later (Wen et al., 2018, Kornhuber et al, 1964), while ERD & ERS present from s before movement up to 1 s after it (Neuper et al.,1996).

We've found in our laboratory previous works that RP amplitude and time length of motor potential are modified when movement conditions change (Becerra et al., 2025). ERS/ERD researches have found that spectral power during conscious movement is modified, condition such as quantity of goals and willingness (Rhodes et al.,2018 , Müller-Putz et al., 2006).

This investigation will allow to create a correlation between RP and ERS/ERD during long duration movements (2 s, 4s, 6 s) as well as observe how time length of movements affect latency for ERS and ERD.

Our experimental data show a decrease in RP amplitude inversely related to duration of movement as well as an increase in latency and duration for ERS after movements proportional to the increase in movement duration.

Disclosures: A. Avalos Salgado: None. H. Galvan Guerrero: None. V. Ramos Scalabrin: None. O. Becerra Casillas: None. L.P. Osuna Carrasco: None. M. Trevino Villegas: None. B. De la torre: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.12/M13

Topic: F.04. Voluntary Movements

Support: R01HD097619
R56MH113627
R01MH119086

Title: Motor Signatures of Context-dependent learning

Authors: *K. UGORJI¹, J. LEE², A. CASAMENTO MORAN³, D. MCNAMEE⁴, V. S. CHIB²;
¹Biomed. Engin., Johns Hopkins, Baltimore, MD; ²Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; ³Physical Med. and Rehabil., Johns Hopkins Univ., Pikesville, MD; ⁴Neurosci., Champalimaud Res., Lisboa, Portugal

Abstract: Motor memories are context-dependent and formed, stored, and retrieved depending on sensory-temporal cues (Smith et al., 2006; Howard et al., 2015). It has been suggested that the nervous system activates the appropriate internal models by inferring the appropriate context for a desired action (Heald et al., 2021), yet the motor and neural signatures of this inference remain poorly understood. Thus, we examined how distinct motor performance metrics reflect context-dependent motor learning. Participants performed repeated isometric hand contractions that were associated with different visual cues with distinct force and time requirements. Force determined the level of exertion required, and time determined the duration of the exertion. On Day 1, participants focused on learning either the force or time dimension of the cue, creating two groups based on this dimension-order: a force-first and time-first group. On Day 2, the focus shifted to the other dimension. By Day 3, some participants had learned the full force-time associations (learners), while others had not (non-learners). Thus, we had four groups- force-first learners, force-first non-learners, time-first learners and time-first non-learners. We extracted three motor metrics from all force traces: (1) force overshoot (peak - steady force), (2) stabilization time (time from when they first reached the target force to when they stabilized at it), and (3) exertion variability (coefficient of variation in force after stabilization). On Day 1, the force-first learners exhibited significantly smaller overshoots and shorter stabilization times compared to the time-first learners and force-first non-learners, indicating context-specific learning. On Day 2, the force-first learners demonstrated savings, as indicated by lower stabilization times, compared to their time-first counterparts, despite being expected to perform worse due to a shift in contextual focus. The non-learners exhibited significantly higher exertion variability on Day 1 than the learners, indicating that greater exertion variability potentially impaired their ability to associate cues with force-time requirements. Preliminary fMRI results revealed stronger force representation in M1 in the force-first learners than in the time-first learners. Collectively, these results suggest that distinct and measurable neuromotor signatures can characterize context-dependent motor learning. Future work will investigate the sensorimotor brain regions responsible for representing these context-driven motor signatures.

Disclosures: K. Ugorji: None. J. Lee: None. A. Casamento Moran: None. D. McNamee: None. V.S. Chib: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.13/M14

Topic: F.04. Voluntary Movements

Support: NIBIB U24EB028998
NYS DOH1-C32250GG-3450000

Title: Motor cortex multiscale mechanistic model tuned to reproduce experimentally-recorded behavioral neural manifolds derived from CEBRA

Authors: *R. BARAVALLE¹, V. BRAGIN^{2,3}, N. NOVIKOV⁴, W. XU⁵, E. URDAPILLETA⁶, I. C. DUGUID⁵, S. DURA-BERNAL¹;

¹Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; ²Dept. of Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. University, Brooklyn, USA, Brooklyn, NY; ³Brain Simulation Section, Charité, Universitätsmedizin Berlin, Berlin, Germany; ⁴Ctr. for Biomed. Imaging & Neuromodulation, Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY; ⁵Univ. of Edinburgh, Edinburgh, United Kingdom; ⁶Inst. Balseiro, Bariloche, Argentina

Abstract: The neural manifold hypothesis states that behavior related activity in the brain lies in low dimensional manifolds, generating both flexible and robust neural representation of diverse activities. In particular, manifolds have been described in the primary motor cortex (M1) during motor behavior. These manifolds are highly consistent across individuals during the same motor task.

The objective of this study is to uncover the origins of latent neural manifolds in mouse M1 during a reaching task. Specifically, we identify the contributing cell types, cortical layers, and biophysical mechanisms underlying these dynamics. To this end, we recorded in vivo spiking activity from neurons in M1 and the ventrolateral thalamus using Neuropixels probes during task performance. To extract the manifolds, we used CEBRA, a tool that employs nonlinear embedding techniques that integrate information across multiple modalities, including spikes, local field potentials (LFPs), and behavioral state.

In previous work, we developed a biologically detailed computational model of primary motor cortex (M1) circuits, incorporating realistic models of corticospinal neurons that convey motor commands to the spinal cord. This model was validated using in vivo spiking and local field potential (LFP) recordings, demonstrating its ability to make accurate predictions. We also found that the model's activity could be captured using low-dimensional manifolds that changed across experimental conditions. In the present study, we extend the M1 model by adding two additional interneuron types and calibrate it to reproduce the specific learned neural manifolds observed in mouse recordings during the reaching motor task, which are capable of decoding behavioral variables with notable accuracy. To add more constraint to the model, we include recorded spikes from the ventrolateral thalamus as an input to the network. To align the M1 model with experimentally observed neural manifolds, we tested multiple strategies, including adjusting long-range inputs within a fixed network configuration and altering circuit connectivity using global optimization techniques.

Reproducing experimental behavior-related neural manifolds in large-scale cortical models enables linking neural dynamics across scales (membrane voltages, spikes, LFPs, EEG) to behavior, experimental manipulations, and disease. This approach helps refine models,

characterize the relationship between latent dynamics and specific cell types, and ultimately deepen our understanding of how brain circuits generate motor behavior.

Disclosures: R. Baravalle: None. V. Bragin: None. N. Novikov: None. W. Xu: None. E. Urdapilleta: None. I.C. Duguid: None. S. Dura-Bernal: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.14/M15

Topic: F.04. Voluntary Movements

Support: R01NS123435

Title: A Non-human primate model for limb selection

Authors: *C. D. HOLMES^{1,2}, S. HONG², S. GEPSHTEIN³, L. H. SNYDER², E. F. MOOSHAGIAN¹;

¹Univ. of California San Diego, San Diego, CA; ²Neurosci., Washington Univ. Sch. of Med., Saint Louis, MO; ³The Salk Inst., La Jolla, CA

Abstract: Primates, like many animals, interact with the environment using their forelimbs. Some actions, such as peeling a banana, require both limbs; but many actions require only one limb and often either limb is sufficient. In these cases, the animal chooses which limb to use. Studies in humans reveal a general ipsilateral limb preference - favoring the left limb for left-side targets and the right limb for right-side targets - and demonstrate key factors such as task demands, movement efficiency, and biomechanical constraints that alter this preference but the neural mechanisms governing limb selection remain poorly understood.

A non-human primate model allows for both behavioral analysis and direct investigation of neural mechanisms. To address the validity of this model, we trained two non-human primates (*Macaca mulatta*) to reach for stimuli on a touch screen. Before each reach, the subject fixated a central point while placing each hand on a "home" button positioned 20 cm in front of the subject at waist level. The reach target then appeared at a random position on the screen and the subject reached for it with one limb to receive a liquid reward. The non-reaching limb remained on its home button while the eyes and the reaching limb were free to move.

As expected, subjects exhibited an ipsilateral limb preference, with a point of subjective equality (PSE) near midline. Reaches across the PSE with the "less preferred" limb were associated with longer reaction times, suggesting a deliberative process.

We examined which parameters influence limb preference by testing three manipulations of starting posture: 1) hand position, 2) head direction, and 3) eye position. All three manipulations shifted the subject's PSE in the same direction as the postural change, suggesting that limb selection is influenced by the body's orientation. These data suggest that limb selection is

influenced by multiple cues, with head orientation playing a particularly strong role. Furthermore, manipulations of limb preference will be critical for probing the neural mechanisms underlying limb selection in future studies.

Disclosures: C.D. Holmes: None. S. Hong: None. S. Gepshtein: None. L.H. Snyder: None. E.F. Mooshagian: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.15/M16

Topic: F.04. Voluntary Movements

Support: R01NS107599

Title: Functional contributions of tongue-jaw motor cortex to innate licking behavior depend on task learning and task difficulty

Authors: *S. KABBARA¹, A. LAM³, E. ZAGHA²;

¹Neurosci., ²Molecular, Cell, and Systems Biol., Univ. of California Riverside, Riverside, CA;

³Div. of Biomed. Sci., Univ. of California, Riverside, Riverside, CA

Abstract: Normal 0 false false false EN-US X-NONE X-NONE /* Style Definitions */
table.MsoNormalTable {mso-style-name:"Table Normal"; mso-tstyle-rowband-size:0; mso-tstyle-colband-size:0; mso-style-noshow:yes; mso-style-priority:99; mso-style-parent:""; mso-padding-alt:0in 5.4pt 0in 5.4pt; mso-para-margin-top:0in; mso-para-margin-right:0in; mso-para-margin-bottom:8.0pt; mso-para-margin-left:0in; line-height:115%; mso-pagination:widow-orphan; font-size:12.0pt; font-family:"Aptos",sans-serif; mso-ascii-font-family:Aptos; mso-ascii-theme-font:minor-latin; mso-hansi-font-family:Aptos; mso-hansi-theme-font:minor-latin; mso-font-kerling:1.0pt; mso-ligatures:standardcontextual;} While it is clear motor cortex plays important roles in task learning and performance, cortical control over innate behaviors remains poorly understood. Here, we investigate the activation and functional contributions of tongue-jaw motor cortex (tjM1) during sensory detection tasks that require licking output. First, we sought to determine the levels of tjM1 activation in different learning stages. Using widefield Ca²⁺ imaging, we imaged dorsal cortex and quantified the licking-aligned activations in both naïve and expert mice. Compared to naïve mice, expert mice exhibited more robust activation in tjM1 preceding and during the lick. Next, we tested the functions of tjM1 in two related tasks with different licking requirements. In the ‘operant task’, mice are required to lick following a target stimulus, but are not penalized for off-target licking. In the ‘impulse control task’, mice also learn to lick following a target stimulus, but they learn to withhold licking at all other times. For both tasks, we suppress tjM1 using GABA_a agonist muscimol in interleaved sessions. We found that tjM1 suppression reduces licking and task performance in the impulse control task to

a greater extent than the operant task. These data demonstrate the differential cortical control of an innate behavior. Furthermore, they suggest that innate behaviors may become increasingly cortically-dependent when embedded in cognitively demanding tasks.

Disclosures: S. Kabbara: None. A. Lam: None. E. Zagher: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.16/N1

Topic: F.04. Voluntary Movements

Support: 5T32HD040127-22
W. M. Keck Foundation Award
Burroughs Wellcome Fund Career Awards at the Scientific Interface

Title: Mapping Distributed Circuits for Rodent Motor Recovery via fMRI and Electrophysiology

Authors: *S. ALBERT¹, J. D. COHEN⁵, C. FREEMAN², M. GERLACH⁶, S. SONG³, L.-M. HSU⁴, M. G. PERICH⁸, J. W. KRAKAUER⁹, Y.-Y. I. SHIH⁷, A. W. HANTMAN¹⁰;
¹UNC Neurosci. Ctr., ²UNC Chapel Hill, Chapel Hill, NC; ³UNC Chapel Hill, Neurology, NC; ⁴Neurol., UNC Chapel Hill, Chapel Hill, NC; ⁵Cell Biol. and Physiol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; ⁶Univ. of North Carolina at Chapel Hill, Cary, NC; ⁷Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; ⁸Dept. of Neurosci., Univ. of Montreal, Montreal, QC, Canada; ⁹Neurol., Johns Hopkins Univ., Baltimore, MD; ¹⁰Cell Biol. and Physiology, Neurosci. Ctr., Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Optogenetic inactivation of the motor cortex paralyzes reach-to-grasp actions in mice. But with prolonged disruption, we discovered that mice can regain past motor function. To elucidate the neural circuit for recovery, we targeted electrodes to forelimb control structures including the caudal forelimb area, rostral forelimb area, striatum, motor thalamus, and interposed nucleus of the cerebellum. Surprisingly, while this distributed population retained arousal-related activity, the kinematic encoding of the reach event itself was absent, suggesting that a new circuit had subsumed motor control. To illuminate its location, we used a silent fMRI technique (SORDINO-fMRI) to image the entire brain as mice executed reach-to-grasp actions in the scanner bore. This approach revealed a whole-brain recovery map that corroborated our electrode recordings, namely, that the motor cortex, striatum, and thalamus contralateral to the limb remained inactive across the recovery timecourse. Instead, recovery was supported by a dramatic upregulation in activity in the opposite hemisphere (ipsilateral to the limb), with sharp enhancements across the ipsilateral motor cortex, striatum, motor thalamus, superior colliculus, and various regions in the pons, brainstem, and cerebellum. To begin interrogating this map, we recorded single unit activity in the ipsilateral motor cortex and observed recovery-related signals

that were absent in the contralateral hemisphere. Further, optogenetic inactivation of the ipsilateral motor cortex partly reversed recovery. Together, our experiments demonstrate that reaching actions are flexibly and robustly supported by parallel contralateral and ipsilateral pathways in the rodent. Deterioration in contralateral control evokes a distributed recovery circuit that partly depends on the ipsilateral hemisphere. Our work shows that fMRI can be applied in rodents in tandem with electrode recordings to reveal the entire scope of recovery circuits.

Disclosures: S. Albert: None. J.D. Cohen: None. C. Freeman: None. M. Gerlach: None. S. Song: None. L. Hsu: None. M.G. Perich: None. J.W. Krakauer: None. Y.I. Shih: None. A.W. Hantman: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.17/N2

Topic: F.04. Voluntary Movements

Support: FQRNT Grant 328238

Title: From planning to correcting: Increased feedback gains are associated with greater beta desynchronization during reach planning

Authors: *D. DELISLE-GODIN, A. DELISLE, P.-M. BERNIER;
Dept. de Kinanthropologie, Univ. De Sherbrooke, Sherbrooke, QC, Canada

Abstract: Humans are highly proficient at making rapid feedback corrections during movement, a capability thought to rely on the engagement of a feedback controller whose gains are tuned to task goals and constraints. Supporting this view, numerous studies have shown that electromyographic (EMG) responses to mechanical perturbations are modulated by task constraints—such as target size—as early as 60 ms post-perturbation. It is widely proposed that the selection of a feedback controller occurs during motor planning, prior to movement onset. In electroencephalography (EEG), motor planning is commonly linked to beta-band activity (13-30 Hz), which reliably desynchronizes before movement. The amplitude of this event-related desynchronization (ERD) is thought to reflect the allocation of neurocomputational resources. Consistent with this interpretation, movements requiring more elaborate planning—such as those performed during early learning, involving complex sequences, or executed at non-preferred speeds—are associated with stronger ERD. Despite these insights, the EEG markers underlying the selection of a feedback controller during motor planning remain unexplored, leaving a gap in our understanding of the neurophysiological mechanisms involved in the tuning of feedback gains. To address this, we recorded EEG and EMG activity from 28 healthy participants (13 male; 19-31 years) as they performed a delayed, goal-directed reaching task toward either a wide

(80 cm; 120 trials) or narrow (2 cm; 120 trials) target. On a subset of trials (40 trials), mechanical perturbations (± 12 N) were applied to measure feedback responses. We hypothesized that EMG responses to perturbations would be greater when reaching toward the narrow target and that beta activity would exhibit stronger desynchronization during the delay period preceding these movements. Consistent with prior work, EMG responses in the R2 epoch (45-75 ms post-perturbation) were significantly larger for the narrow target: in the pectoralis for the +12 N perturbation ($p < 0.001$) and in the posterior deltoid for the -12 N perturbation ($p = 0.002$). A cluster-based permutation analysis of EEG data revealed significantly greater beta ERD broadly over bilateral parieto-frontal scalp sites during the delay period for the narrow target condition ($p = 0.002$). Together, these findings replicate established evidence that feedback responses are modulated by task accuracy constraints and demonstrate for the first time that this modulation is preceded by increased beta ERD, suggesting enhanced neurocomputational resource allocation during the setup of a feedback controller with increased gains.

Disclosures: **D. Delisle-Godin:** None. **A. Delisle:** None. **P. Bernier:** None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.18/N3

Topic: F.04. Voluntary Movements

Support: F32NS131217

Title: Selective coupling-decoupling prepares motor network for precise motor action

Authors: ***S. M. LEMKE**¹, J.-Z. GUO¹, S. APPAQAQ¹, A. W. HANTMAN²;
²Cell Biol. and Physiology, Neurosci. Ctr., ¹Univ. of North Carolina, Chapel Hill, NC

Abstract: The brain is fundamentally interconnected. The neural control of movement exemplifies distributed function - disrupting neural dynamics across many cerebral and cerebellar brain regions can each disrupt the production of skilled movement. However, how these cerebral and cerebellar areas interact to produce skilled movements remains unclear. It is possible that skilled motor control requires complex cross-area interactions between all motor areas at the supraspinal level. Alternatively, individual areas (or subsets of areas) may function independently with common outputs converging on premotor structures in the brainstem and spinal cord. Here, we use multi-site single-neuron neurophysiology to demonstrate an interplay of cross-area coupling and decoupling between movement-informative and non-informative neuron subpopulations during the period preceding movement execution. These network dynamics are predictive of the quality of upcoming movements and disrupting these dynamics deteriorates upcoming movement quality. These results highlight the importance of separating movement informative and non-informative cross-area neural dynamics to understand the

complex network interplay that underlies precise motor action. We next show that coupling and decoupling are associated with distinct oscillatory rhythms observable in cross-area local field potential signals, suggesting that cross-area oscillatory entrainment underlies observed cross-area coupling, rather than changes in firing rate. We also observe pupil diameter also covaries with coupling, suggesting a potential role for neuromodulators. Lastly, we test the generalizability of these network dynamics, examining how they change when mice are tasked with performing distinct motor tasks. This shows that these dynamics are relevant to context in which multiple actions need to be performed, and that movement-informative and non-informative populations can be dynamically recruited based on context. In summary, we provide evidence that complex and selective network interactions across widespread cerebral and cerebellar areas are essential to drive precise motor action.

Disclosures: S.M. Lemke: None. J. Guo: None. S. Appaqaq: None. A.W. Hantman: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.19/N4

Topic: F.04. Voluntary Movements

Support: NIH R21-NS113613
NSF CRCNS Japan-US 2113096
Wu Tsai Human Performance Alliance at Stanford University

Title: The Neural Dynamics during Reach-to-Precision-Grasp Behavior Emerges from Nonlinear Recurrent Cortical Activity

Authors: *M. AZADJOU¹, R. PHILIPP⁴, M. ABBASI SISARA², K. SEKI⁵, F. J. VALERO-CUEVAS³;

¹Alfred E Mann Dept. of Biomed. Engin., ²USC, Los Angeles, CA; ³Biomed. Engin., USC, La Crescenta, CA; ⁴Dept. of Neurophysiol., Natl. Inst. of Neuroscience, NCNP, Kodaira, Japan;

⁵Natl.inst.Neurosci., Tokyo, Japan

Abstract: Sensorimotor control arises from complex, dynamic, and often nonlinear interactions between sensory and motor cortical regions. While traditional models of functional connectivity offer insight into directional communication between regions such as the primary motor cortex (MI), somatosensory cortex (SI), and supplementary motor area (SMA), they make the fundamental assumptions of linear and non-recurrent mappings and history-independent point processes. Yet, motor behavior---especially in the context of dexterous, goal-directed actions like reach-to-precision-grasp---is driven by recurrent interactions across these areas, evolving over time with changing neuromechanical and sensory demands and events. To address these limitations, we apply a Recurrent Neural Network (RNN) approach capable of capturing the

spatiotemporal dynamics between MI, SI, SMA, and muscles recordings during a structured reach-to-precision-grasp task. Using simultaneously recorded electrocorticography (ECoG) from MI, SI, and SMA, and electromyography (EMG) from forearm and upper arm muscles in Macaque monkeys, we trained RNNs to learn the sequential structure of these cortical-muscular interactions. Unlike conventional linear methods (e.g., coherence), RNNs allow the extraction of hidden states that encode both nonlinear and temporally recursive dependencies. We hypothesize that these hidden recurrent states will reflect internal representations of evolving control strategies, shaped by task phase and sensory context. By modeling the evolution of cortical interactions through time, our findings offer a novel computational window into sensorimotor integration and may inform the design of adaptive neuroprosthetic systems, precision neuromodulation therapies, and next-generation brain-machine interfaces.

Disclosures: **M. Azadjou:** None. **R. Philipp:** None. **M. Abbasi Sisara:** None. **K. Seki:** None. **F.J. Valero-Cuevas:** None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.20/N5

Topic: F.04. Voluntary Movements

Support: Weill Neurohub

Title: Changes in cervical spinal cord dynamics during recovery from motor cortex inhibition

Authors: ***F. APARICIO**¹, A. SEIELSTAD², S. ARROYO³, L. LUAN⁴, K. GANGULY³; ²Neurol., ¹Univ. of California San Francisco, San Francisco, CA; ³Neurol., UCSF, San Francisco, CA; ⁴Rice Univ., Houston, TX

Abstract: **Changes in cervical spinal cord dynamics during recovery from motor cortex inhibition** Francisco Aparicio^{1,2}, Ruben Contreras-Lopez², Alex Seielstad², Sergio Arroyo^{2,4}, Chong Xie⁵, Lan Luan⁵, Karunesh Ganguly^{1,2,3,4} Department of Neuroscience¹, Department of Neurology², U.C. San Francisco. Department of Neurology and Rehabilitation³, V.A. Medical Center, San Francisco⁴, Rice Neuroengineering Initiative, Rice University⁵ **Abstract** The spinal cord (SC) is a key hub in the motor system as it receives and integrates inputs from multiple motor related brain regions to produce movement. Anatomical and lesion studies looking at the structural and functional connectivity of motor circuitry, identified the motor cortex as key area that dynamically modulate movements via projections to the spinal cord. However, because of the technical hurdles associated with performing electrophysiology recordings from the spinal cord, it is unclear how cortical inputs modulate spinal network activity to drive forelimb movements. Here we performed experiments, in mice, to elucidate movement related spinal activity patterns and how these population activity patterns change in the absence of cortical

input. Using Neuropixels 2.0 probes we recorded neuronal activity across the intermediate and ventral horns of the C5-C6 spinal segments in head-fixed mice performing a cue-driven forelimb lever push task, we characterized spinal population dynamics before, during, and after inhibition of the motor cortex. Our analyses revealed that spinal neural activity during forelimb movements occupies a low-dimensional manifold, reflecting coordinated population dynamics. A subset of spinal neurons exhibited firing patterns tightly aligned with movement kinematics during task execution. Upon cortical inhibition with muscimol, these structured activity patterns were disrupted, indicating a critical role of cortical input in shaping spinal dynamics. Interestingly, we observed a recovery of the spinal population activity structure in trials following cortex inhibition; preliminary analysis suggests a non-linear pattern of recovery. Our findings demonstrate that cortical input (either direct or via subcortical regions) exert a temporally precise and non-linear influence on spinal population activity.. Our study provides novel insights into the spinal neural activity underlying skilled movement and highlights how disruption of cortical input—such as that seen in stroke—alters these dynamics. Funding: Weill Neurohub

Disclosures: F. Aparicio: None. A. Seielstad: None. S. Arroyo: None. L. Luan: None. K. Ganguly: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.21/N6

Topic: F.04. Voluntary Movements

Title: Individual differences in motor variability in relation to thalamic and M1 GABA content

Authors: *R. RUOPP¹, M. GACH², I. GREENHOUSE²;

¹Biol., Inst. of Neurosci. - Univ. of Oregon, Eugene, OR; ²Human Physiol., Univ. of Oregon, Eugene, OR

Abstract: The thalamus may serve a special role in decreasing motor variability during the transformation of actions from controlled to automated. It acts as a circuit bottleneck, receiving GABA-ergic inhibitory input from a variety of regions before relaying motor commands to cortex. This architecture is hypothesized to suppress competing motor representations during action selection and to filter out task-irrelevant neural noise. Here, we compared individual differences in motor variability during the performance of a highly automated skill (keyboard typing) to thalamic GABA levels measured via MEGA-PRESS single-voxel edited H1 magnetic resonance spectroscopy (MRS) at 3T. The primary motor (M1) and occipital (OCC) cortices were included as additional MRS voxels of interest.

Healthy participants (n = 47, 21±2.9 years old, 25 female) typed five-letter strings selected from an American English lexicon. Bigrams (two-letter sequences) within strings were grouped into three levels (low, medium, high) based on naturally occurring frequency. Interkey Interval (IKI),

the time between the start of two consecutive keystrokes, was calculated for all bigrams. Standard deviation (SD) and coefficient of variation (CV) of IKI were calculated for each frequency category and participant to assess motor variability. Mean IKI SD and CV differed significantly across bigram frequencies [(F(92)=144.3 and (F(92)=34.5, p's<.001].

GABA+ was measured from MRS voxels in the left and right thalamus (35x35x20mm; n = 11), left and right M1 (25x25x25mm; n = 21), and bilateral OCC (25x25x25mm; n = 21). Voxel-wise MRS GABA+ estimates were compared with IKI SDs and CVs for the three bigram frequency levels using Pearson correlations corrected for multiple comparisons. Differences in IKI SDs and CVs from high to low frequency categories were also compared with GABA+. No comparisons were significant, suggesting that the capacity for thalamic and cortical inhibition do not correlate with individual motor variability levels and reductions during production of automated action. Data collection is ongoing in a larger sample. This work shows proof of concept of a novel technique for assessing individual differences in both local GABA content and motor skill variability in humans with high ethological validity.

Disclosures: R. Ruopp: None. M. Gach: None. I. Greenhouse: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.22/N7

Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS121409
NIH Grant U19NS137920

Title: The influence of motor cortex cell types on subcortical motor planning and execution dynamics

Authors: J. E. BIRNBAUM^{1,2}, *O. EL SAYED^{1,3}, J. UGARTE NUNEZ¹, D. PALMER¹, B. DEPASQUALE³, M. N. ECONOMO^{1,3};

²Grad. Program in Neurosci., ³Dept. of Biomed. Engin., ¹Boston Univ., Boston, MA

Abstract: Goal-directed behavior relies on the seamless integration of cognitive and motor processes across brain regions. The motor cortex (MC) plays a central role in the planning and execution of goal-directed movements through its descending projections to subcortical motor areas via pyramidal tract (PT) neurons. Prior work identified two PT subtypes—PTUpper and PTLower—that differ in their anatomical projection targets and physiology; PTUpper cells project to the thalamus and exhibit early-onset preparatory activity during sensory-guided behavior, while PTLower cells project to the medulla and display action-related activity. Both subtypes also share several projection targets to subcortical areas involved in both planning and execution, raising the question of how the MC influences downstream neural dynamics related to

these processes via these two anatomical pathways. To address this, we combined cell-type specific optogenetic silencing, Neuropixels recordings in the MC and several subcortical regions, and high-speed videography in mice performing a delayed-response licking task, in which they must plan and execute a directional tongue movement based on an auditory cue. To assess how PTUpper vs. PTLower perturbations affect population dynamics, we identified neural dimensions associated with motor planning and action in each recorded region. Preliminary analyses suggest that perturbations of different PT types produce distinct behavioral deficits and differentially affect dynamics in downstream structures, with PTLower neurons related specifically to the planning and execution of the kinematics of movements, and PTUpper neurons related to the selection and execution of actions, defined categorically. Identifying the roles of PT subtypes can further our understanding of the pathways through which the MC influences cortical and subcortical dynamics underlying sensory-guided behavior.

Disclosures: J.E. Birnbaum: None. O. El Sayed: None. J. Ugarte Nunez: None. D. Palmer: None. B. DePasquale: None. M.N. Economo: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.23/N8

Topic: F.04. Voluntary Movements

Support: RO1NS108424

Title: Introductory notes as motor preparatory motor gestures underlying zebra finch song

Authors: *S. ASADOORIAN¹, K. BIEN¹, A. R. MAGEE¹, J. MENDEZ², B. G. COOPER¹;
¹Psychology, Texas Christian Univ., Fort Worth, TX; ²Physics, Minnesota State Univ., Mankato, MN

Abstract: Humans exhibit complex, learned, sequential motor behaviors, such as speech, and playing musical instruments; motor actions like these require planning and preparation before movement onset. The zebra finch (*Taeniopygia guttata*) vocal display (song) is learned by juveniles through imitation of adult conspecifics. Song production is studied because of the numerous parallels with human speech and language. The zebra finch song consists of a stereotyped sequence of 4-7 song syllables (motif); the motif may be repeated multiple times forming a song bout. Zebra finches sing a sequence of introductory notes that become increasingly stereotyped as they progress toward the first song motif. Introductory notes have been hypothesized to function as a form of motor preparation to enable precisely stereotyped song production. However, experimental tests of this hypothesis have not yet been conducted. Here we experimentally test the role of introductory notes as a preparatory motor act, by presenting a 100 ms long white-noise burst at a low or high intensity (65 or 95 dB) in 12 birds.

The sound stimulation was presented during the production of introductory notes and different times during the song bout. We predicted that if introductory notes are a preparatory motor program, a disruptive stimulus would preferentially interrupt introductory notes, as compared to the motif or song bout motor patterns. We quantified the percentage of introductory note interruption (delays in song execution) and song termination (cessation of the song before completing the typical syllable sequence). Low-amplitude (65 dB) sound presentation interrupted the introductory note sequence in 81% of the trials, whereas song termination was observed in only 5% of the first motifs, and 30% of the trials when presented during subsequent motifs. We found that song could be reliably interrupted by the presentation of a high-amplitude white noise burst. In the high-amplitude trials, motor interruption was observed in 67% of the introductory notes, and song cessation was observed in 60% of the trials when presented during the first motif, and 30% of the trials during the subsequent motifs. The pronounced susceptibility of the introductory notes to external stimulation compared to the song motor pattern is consistent with the preparatory hypothesis. Understanding motor planning and preparation can provide insight into neurological, behavioral, speech, and motor language disorders that are characterized by deficits in neuromuscular preparation.

Disclosures: S. Asadoorian: None. K. Bien: None. A.R. Magee: None. J. Mendez: None. B.G. Cooper: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.24/N9

Topic: F.04. Voluntary Movements

Support: UG3-MH129381 from NIMH

Title: Quantifying Hand Motor Behavior Following Intramuscular DCZ Administration in Rhesus Macaques Using Pose Estimation Software

Authors: *J. I. MEJAES¹, F. A. MUNOZ², J. P. WILLI¹, V. P. FERRERA¹;
¹Neurosci., Columbia Univ., New York, NY; ²Columbia Univ., NEW YORK, NY.

Abstract: Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are a powerful tool for selectively modulating neural activity in nonhuman primates. Deschloroclozapine (DCZ), a potent and selective DREADD agonist, is increasingly used due to its high receptor affinity and rapid onset. However, understanding DCZ's baseline effects in the absence of DREADD expression is critical for interpreting chemogenetic results, particularly when motor behavior is a primary outcome. While most studies use systemic administration, the behavioral impact of intramuscular (IM) DCZ remains poorly characterized. This study assessed the baseline motor effects of IM-administered DCZ in two rhesus macaques

(one male, one female) performing a battery of structured motor tasks, including a center-out reaching task, circular-out reaching task, a repetitive-corner reaching task, and a controlled foraging task. Each animal received three DCZ doses (0.0 mg/kg [vehicle], 0.1 mg/kg, and 0.3 mg/kg) in a within-subject, counterbalanced design. At this stage, only baseline (non-DREADD) DCZ data has been collected and analyzed. Across conditions, noconsistent dose-dependent changes in task performance were observed, suggesting minimal off-target motor effects at the tested doses.

To further quantify hand motor behavior, we also employed a markerless pose estimation software that allows frame-by-frame tracking of hand position during task performance. This approach enables detailed analysis of movement kinematics, including velocity, trajectory, and movement smoothness, and can detect subtle motor abnormalities such as tremor. Video recordings from each session were analyzed to determine whether higher doses of DCZ produce detectable changes in hand movement dynamics.

These findings establish an important behavioral baseline for interpreting future chemogenetic manipulations involving DREADD expression in studies of motor control. By characterizing the effects of DCZ alone, this work supports more accurate attribution of motor changes to targeted neural modulation in nonhuman primates.

Supported by UG3-MH129381 from NIMH

Disclosures: J.I. Mejaes: None. F.A. Munoz: None. J.P. Willi: None. V.P. Ferrera: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.25/N10

Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS129098
NIH Grant R01NS129584
NSF Grant DRL2124066
NSF Grant DRL2123911

Title: Subjective preference is encoded in the motor cortex

Authors: *H. MIYATA¹, R. H. CHOWDHURY⁴, A. L. SMOULDER⁶, M. ZAMBRE⁵, J. WEN², E. R. OBY⁵, A. P. BATISTA⁴, S. M. CHASE³;

¹Carnegie Mellon Univ., PITTSBURGH, PA; ³Neurosci. Inst., ²Carnegie Mellon Univ., Pittsburgh, PA; ⁴Bioengineering, ⁵Univ. of Pittsburgh, Pittsburgh, PA; ⁶Dept. of Biomed. Engin., Boston Univ., Boston, MA

Abstract: The primate motor cortex (MC) is traditionally known for its involvement in planning and executing movements. However, neurons in MC are also modulated by reward: movement

preparatory signals in MC depend on the reward to be received. Here we investigate the nature of this modulation, and provide three lines of evidence for the presence of a unitary “motivational signal” in the motor cortex. A monkey learned to associate visual cues with different reward magnitudes (small, medium, large) and probabilities (guaranteed, frequent, rare) during a delayed reaching task. We recorded motor cortex activity during the planning period after cue presentation. Our first line of evidence for a motivation signal comes from our observation that neural population analyses at the end of the delay period revealed that both reward magnitude and probability were encoded along a single dimension—which we term the “motivation axis”—that captured approximately 90% of the motivation-related variance. This suggests that MC integrates multiple motivational factors, rather than representing them separately. Second, we found that the motivation axis only partially matched up with expected reward—this suggests that other cognitive factors are at play here. We asked whether the motivation axis reflected cognitive factors such as subjective preferences. We introduced choice trials in which an animal indicated their preferences between different combinations of reward magnitude and probability. Neural activity along the motivation axis strongly correlated with the animal’s subjective preferences. This suggests that MC encodes motivation as subjective value. Separately, day-to-day projections onto the motivation axis predicted daily shifts in preference. For each session, we performed an ROC analysis on trials involving offer pairs that had the same expected reward, computing the area under the curve (AUC) for the neural activity along the motivation axis. The resulting AUC was strongly correlated with the day-by-day changes in choice preferences. These findings indicate that MC dynamically mirrors the animal’s day-to-day motivational state. Third, we varied reward types (water or fruit juice) and reward magnitudes within the same delayed-reach task. Two monkeys showed greater projection along the motivation axis for juice over water, consistent with their day-by-day preferences. In summary, our results show that MC integrates motivational variables into a unified, subjective preference signal. This expands the traditional view of MC beyond merely specifying movement goals and commands: MC is sensitive to myriad variables that shape how we move, as a function of motivation.

Disclosures: H. Miyata: None. R.H. Chowdhury: None. A.L. Smoulder: None. M. Zambre: None. J. Wen: None. E.R. Oby: None. A.P. Batista: None. S.M. Chase: None.

Poster

PSTR027: Motor Planning and Execution: Behavior and Neurophysiology: Human and Non-Humans

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR027.26/N11

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI JP24KJ1982
JSPS KAKENHI JP23K27943
JSPS KAKENHI JP22H03442

Title: Selective modulation of the StartReact response by conditioning transcranial magnetic stimulation over the supplementary motor area

Authors: *N. KATAGIRI^{1,2,3}, T. YAMAGUCHI^{4,5}, K. TAKANO^{1,3}, T. SATO², S. TANABE⁶, T. FUJIWARA^{1,5};

¹Juntendo Univ. Grad. Sch. of Med., Tokyo, Japan; ²Tokyo Bay Rehab. Hosp., Narashino, Japan; ³JSPS, Tokyo, Japan; ⁴Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; ⁵Juntendo Univ. Grad. Sch. of Hlth. Sci., Tokyo, Japan; ⁶Sch. of Hlth. Sci., Fujita Hlth. Univ., Toyoake, Japan

Abstract: The reticulospinal tract is crucial for coordinating movements, particularly regulating muscle tone, posture, and balance. The corticoreticular pathway, originating from the supplementary motor area (SMA) and primary motor cortex (M1), is thought to modulate this reticulospinal output. However, the modulation by cortical inputs is still not fully understood. StartReact—a phenomenon in which reaction times are shortened by startling acoustic stimuli—has been proposed as a noninvasive index of reticulospinal excitability (Akalu, 2023). To examine the temporal profile of corticoreticular modulation, we applied single-pulse transcranial magnetic stimulation (TMS) over the SMA or M1 at varying interstimulus intervals (ISIs) preceding a visual cue, and measured StartReact responses. Three experiments were conducted: Experiment 1 tested short-latency SMA effects; Experiment 2 targeted long-latency SMA effects; and Experiment 3 assessed long-latency M1 modulation. Ten healthy participants (three females, mean age 24 ± 2 years) took part in Experiments 1 and 2, and seven in Experiment 3. Reaction times for rapid knee extension were recorded in response to a visual cue alone (visual reaction time [VRT]) or combined with a 112 dB startling acoustic stimulus (visual startle reaction time [VSRT], i.e., StartReact response). Surface electromyography was recorded from the left rectus femoris. TMS was delivered at 140% of the active motor threshold over SMA (4 cm anterior to Cz) or M1 (Cz), depending on the experiment. ISIs between TMS and the visual cue varied by experiment: 0 to 6 ms (in 1 ms steps) in Experiment 1, and 0, 4, 10, 15, 30, 50, and 100 ms in Experiments 2 and 3. Reaction times were averaged across 10 trials per condition and analyzed using a mixed-model repeated-measures analysis of variance with ISI as a within-subject factor ($\alpha = .05$, Bonferroni-corrected). A significant main effect was observed for VSRT in Experiment 2 ($F_{[6,54]} = 4.872$, $p < .01$). Post hoc comparisons revealed that VSRTs were significantly shorter at ISIs of 30 ms and 50 ms compared to 0 ms (both $p < .01$). In addition, a significant main effect was found for VRT in Experiment 3 ($F_{[6,36]} = 3.228$, $p = .012$), although no significant post hoc differences were detected (all $p > .05$). No significant main effects were observed for VSRT in Experiments 1 or 3, nor for VRT in Experiments 1 or 2 (all $p > .05$). These results suggest that StartReact responses can be selectively facilitated by TMS over SMA at ISIs of 30 and 50 ms, pointing to temporally specific corticoreticular interactions. This approach may serve as a potential indicator of corticoreticular excitability.

Disclosures: N. Katagiri: None. T. Yamaguchi: None. K. Takano: None. T. Sato: None. S. Tanabe: None. T. Fujiwara: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.01/N12

Topic: F.09. Motor Neurons and Muscle

Support: Paralyzed Veterans of American Research Foundation Grant #3186

Title: Intensity- and frequency-dependent effects of transcutaneous spinal stimulation on spasticity in chronic spinal cord injury

Authors: *A. LATIMER¹, E. GORDINEER², D. S. STOKIC³, K. E. TANSEY⁴, M. J. KRENN⁵;

¹Univ. of Mississippi Sch. of Med., Jackson, MS; ²Univ. Of Mississippi Med. Ctr. Grad. Program In Neurosci., Jackson, MS; ³Methodist Rehabil. Ctr., Jackson, MS;

⁴Research/Neurosurg & Neurobio/SCI Clin., Methodist Rehab/U Mississippi Med. Ctr/Jackson VA, Jackson, MS; ⁵Neurosurg., Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Spasticity is a common and disabling consequence of spinal cord injury (SCI), characterized by chronic hyperexcitability of spinal motor circuits that manifests clinically as hyperreflexia, involuntary movements, and increased muscle tone. The imbalance between residual descending inhibition and spinal excitation impacts voluntary movements and may impede performance of activities of daily living, such as dressing, ambulation, and personal hygiene. In recent years, electrical neuromodulation using transcutaneous spinal stimulation (TSS) has emerged as a promising intervention for SCI. In this study, we investigated the short- and long-term neuromodulation effects of different TSS intensities and frequencies on reducing spasticity after SCI. Eight adults with chronic SCI received TSS through a 5 x 5 cm surface electrode centered over T11/T12 and a 15 x 10 cm electrode placed on the lower abdomen. In separate sessions, each participant underwent 30-minute stimulation of each combination of intensity (0.45x and 0.90x the individual's lowest reflex threshold, LRT) and frequency (50 Hz and 100 Hz). Spasticity was evaluated using the Modified Ashworth Scale (MAS) and the Spinal Cord Assessment Tool for Spastic Reflexes (SCATS). The short-term effects were evaluated before and immediately after a single 30-minute TSS session. Long-term effects were assessed after one week of daily home-based TSS sessions. Across all TSS conditions, we found a significant short-term decrease in MAS. The pre- to post-intervention changes in the MAS sum score were most prominent at the intensity of 0.9xLRT and frequency of 100Hz (mean difference -2.75 points, CI_{95%}: -4.46, -1.03). The same combination of intensity and frequency also resulted in the greatest reduction of the SCATS scores; however, the difference was not statistically significant (-1.00 point, CI_{95%}: -1.77 -0.23). In contrast, the long-term effects of TSS on MAS and SCATS were negligible across all conditions. The results suggest that higher TSS frequencies and intensities produce the largest immediate decrease in spasticity without apparent carryover or cumulative effects after seven daily sessions. These exploratory findings suggest that TSS neuromodulation may be a viable short-term therapeutic option for managing spasticity, providing an alternative to systemic pharmacological treatments.

Disclosures: A. Latimer: None. E. Gordineer: None. D.S. Stokic: None. K.E. Tansey: None. M.J. Krenn: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.02/N13

Topic: F.09. Motor Neurons and Muscle

Support: Wings for Life Spinal Cord Research Foundation, WFL-US-07/19:199

Title: Intensity of Transcutaneous Spinal Stimulation Suppresses Multisegmental Posterior Root Reflexes More than Frequency or Passive Stepping in Humans with Spinal Cord Injury.

Authors: *M. J. KRENN^{1,3}, E. GORDINEER⁴, B. SULLIVAN^{2,3}, D. S. STOKIC³;

¹Neurosurg., ²Grad. Studies in the Hlth. Sciences, Program in Neurosci., Univ. of Mississippi Med. Ctr., Jackson, MS; ³Ctr. for Neurosci. and Neurolog. Recovery, Methodist Rehabil. Ctr., Jackson, MS; ⁴Neurosurg., Univ. Of Mississippi Med. Ctr., Jackson, MS

Abstract: Background: Continuous transcutaneous spinal stimulation (TSS) can modulate spinal circuitry and is being explored as a non-invasive intervention to reduce spasticity after spinal cord injury (SCI). However, the dose-response profile of TSS remains insufficiently characterized, particularly the interplay between stimulation intensity and frequency in shaping spinal excitability in the presence or absence of innate afferent input. Objective: To determine how different combinations of TSS intensity and frequency affect the suppression of multisegmental posterior-root reflexes (PRR) at rest and during passive stepping in chronic SCI. Methods: Twenty individuals with SCI (8 AIS A/B, 12 AIS C/D) were recruited at a median of 2.7 (IQR: 1.7, 4.8) years post-injury. TSS was applied with the electrodes over T11/12 (5 x 5 cm) and the abdominal wall (15 x 10 cm). The effects of continuous TSS at three intensities (0.8, 1.0, and 1.2 times the individual lowest reflex threshold) and four frequencies (10, 20, 40, 80 Hz) were assessed using short-latency PRRs. The PRRs were recorded from eight leg muscles, bilaterally, in rest and during robotic passive stepping, midway between leg extension (knee angle 15 deg) and flexion (knee angle 45 deg). The peak-to-peak amplitudes of the conditioned PRRs were normalized to the baseline amplitudes. Results: Linear mixed-effects analysis indicated a dominant main effect of TSS intensity ($p < .001$) and a weaker effect of frequency ($p = .02$), whereas the effects of passive stepping condition and its interaction with either factor were not significantly different. At the highest TSS intensity and 80 Hz frequency, PRRs were suppressed by 53.4% (CI_{95%}: 51.6%, 55.1%), compared to 17.2% (CI_{95%}: 15.6%, 18.8%) at the lowest intensity and 10 Hz. Passive stepping alone resulted in a 19% reduction in PRRs across the midway of leg extension/flexion. When combined with TSS, stepping provided only a marginal additional suppression of 5.5% at the lowest intensity and 0.23% at the highest intensity. Conclusions: Continuous lumbosacral TSS primarily depresses PRR excitability through an intensity-dependent mechanism, with frequency playing a secondary role. Innate afferent input from passive stepping produces PRR suppression comparable to a low-dose TSS. However, when combined with TSS, there is minimal to no additional effect, suggesting that especially high-intensity TSS may saturate the suppressive effects. Thus, supra-threshold TSS

intensities should be prioritized as a treatment strategy for spasticity, provided that PRR suppression reflects the potential for reducing spasticity in individuals with chronic SCI.

Disclosures: M.J. Krenn: None. E. Gordineer: None. B. Sullivan: None. D.S. Stokic: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.03/N14

Topic: F.09. Motor Neurons and Muscle

Title: Changes in the posterior root reflexes and the flexion withdrawal reflexes with different frequencies of transcutaneous spinal stimulation in humans with spinal cord injury.

Authors: *B. SULLIVAN^{1,4}, A. LATIMER², D. S. STOKIC⁴, M. J. KRENN^{3,4};
²Sch. of Med., ³Neurosurg., ¹Univ. of Mississippi Med. Ctr., Jackson, MS; ⁴Ctr. for Neurosci. and Neurolog. Recovery, Methodist Rehabil. Ctr., Jackson, MS

Abstract: Background: Electrical neuromodulation using transcutaneous spinal stimulation (TSS) can modulate spinal circuitry. However, the effect of different frequencies of TSS on mono/oligo- and poly-synaptic reflex pathways remains unexplored. Objective: To determine how different TSS frequencies modulate multisegmental posterior-root reflexes (PRR) and the flexion withdrawal reflex (FWR). Methods: Eight individuals with SCI (4 AIS A/B, 4 AIS C/D) were recruited with a post-injury range of 0.6 to 9.3 years. TSS was applied with a self-adhesive surface electrode array with 3x8 contact pads (outer dimension 4.2x12 cm, contact pad 0.9x0.9 cm) centered midline over the T12 spinal processes, allowing the selection of the array rows yielding the lowest reflex threshold across multiple muscles. Two large 8x13 cm electrodes were placed paraumbilically and interconnected to serve as a reference electrode. The effects of 15-minute neuromodulation with TSS at a frequency of 30 or 75 Hz at the intensities of 0.9 times the individual's lowest reflex threshold were assessed using PRRs and FWR. The test PRRs were evaluated before and during the 15-minute TSS in 8 lower extremity muscles using the same array montage. For PRRs, the area under the recruitment curve (AURC) was calculated from 20 responses. The test FWR was elicited by a cathode (diameter 1 cm) over the medial arch of the foot and a large anode (5x5 cm) placed on the dorsum of the foot. From the four collected responses in the tibial anterior muscle, the area under the curve (AUC) was averaged. Results: The change in PRR-AURC during TSS was not significantly different between 30 Hz and 75 Hz across all muscles (e.g., in TA, 91% (SD=27%) of baseline at 30 Hz and 94% (22%) at 75 Hz, paired-t test: $p = .54$). In contrast, the FWR-AUC showed an increase to 205% (229%) at 30 Hz and a decrease to 81% (41%) at 75 Hz, which was significantly different (paired-t test: $p = .03$). Conclusions: With the near-threshold stimulation intensity, the change in PRR was modest, regardless of the wide range of applied TSS frequencies. However, the FWR appears to be more

sensitive to different TSS frequencies, with lower frequencies producing facilitation and higher frequencies producing suppression.

Disclosures: B. Sullivan: None. A. Latimer: None. D.S. Stokic: None. M.J. Krenn: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.04/N15

Topic: F.09. Motor Neurons and Muscle

Support: Midwestern University Outsourcing Funds

Title: Impact of Bisphenol A (BPA) on the Neuromuscular Synapse

Authors: S. GAONKAR¹, H. GERBS¹, K. DINOVO², *I. MARTINEZ-PENA Y VALENZUELA¹;

¹Midwestern Univ., Downers Grove, IL; ²Midwestern Univ., DOWNERS GROVE, IL

Abstract: Bisphenol A (BPA) is an industrial chemical widely used to manufacture plastics, particularly polycarbonates and epoxy resins. Due to its ability to mimic estrogen and interfere with hormonal signaling, BPA is recognized as a potent endocrine disruptor. While extensive research has documented its systemic effects on various organs, its impact on the peripheral nervous system (PNS), specifically, the neuromuscular junction (NMJ), remains underexplored. The NMJ plays a critical role in facilitating communication between motor neurons and skeletal muscle fibers, making it essential for voluntary movement and coordinated muscle function. BPA exposure has been shown to cause metabolic disturbances such as impaired homeostasis and insulin resistance in skeletal muscle. However, there is limited evidence regarding its influence on skeletal muscle structure or NMJ integrity. In this study, male and female non-Swiss albino mice aged 3 and 6 months were exposed to BPA through dietary intake. The sternomastoid, diaphragm, extensor digitorum longus, and soleus muscles were subsequently analyzed. In males, BPA exposure resulted in mild motor impairments, significant alterations in circulating levels of alkaline phosphatase and triglycerides, and earlier degradation of acetylcholine receptors (AChRs) at the NMJ compared to females. Furthermore, histological examination revealed sex-dependent alterations and muscle atrophy in BPA-exposed male mice. Notably, the Type I slow-twitch fibers in the soleus muscle were spared in both male and female BPA-exposed mice. These findings demonstrated that BPA exerts detrimental effects on both skeletal muscle and the NMJ, with more extensive muscular disruptions observed in males.

Disclosures: S. Gaonkar: None. H. Gerbs: None. K. DiNovo: None. I. Martinez-Pena y Valenzuela: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

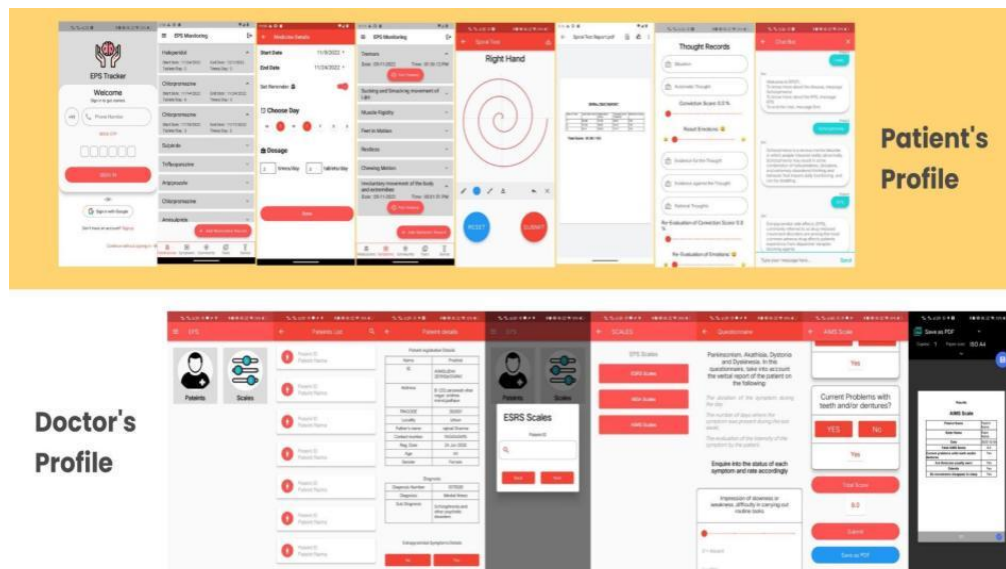
Program #/Poster #: PSTR028.05/N16

Topic: F.09. Motor Neurons and Muscle

Title: Epstr: digital health solution for eps tracking and clinical decision support

Authors: *M. SHARMA;
IIT-AIIMS Jodhpur, Jodhpur, India

Abstract: EPSTr (Extrapyramidal Symptoms Tracker) is a cross-platform mobile application developed using the Flutter framework (Dart), designed to support the diagnosis, monitoring, and long-term management of extrapyramidal symptoms (EPS) in patients with psychiatric disorders. EPS, often induced by antipsychotic medications, are frequently underreported and inadequately tracked, leading to compromised patient outcomes. EPSTr addresses this clinical gap by offering a digital, interactive, and AI-supported solution that empowers both patients and clinicians. The application features secure, role-specific access for patients, guardians, and healthcare professionals. Patients can log symptoms, track medications, perform psychometric and motor assessments (e.g., spiral tests), and communicate with clinicians in real-time. Clinicians can access structured medical histories, view longitudinal symptom trends, utilize EPS rating scales, and receive AI-generated risk predictions to optimize treatment plans. A built-in prediction module uses machine learning to forecast EPS likelihood based on patient history and medication profiles. The app also includes multilingual chatbot support for EPS education and awareness. By integrating digital health tools with predictive analytics and facilitating doctor-patient engagement, EPSTr advances the standard of psychiatric care, enhances early detection of side effects, and improves treatment safety and efficacy.



Disclosures: M. Sharma: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.06/O1

Topic: F.09. Motor Neurons and Muscle

Support: FRAXA Research Foundation Fellowship
NIA R21AG078909

Title: Initial steps toward developing a workflow paradigm to deploy spatial transcriptomics to define gene expression profiles in denervated human muscle using muscle biopsies obtained intra-operatively

Authors: *P. S. PIRBHOY¹, V. MURUGAN³, C. LEE⁴, R. GUPTA², O. STEWARD⁵;

¹Anat. and Neurobio., ²Orthopaedic Surgery, Univ. of California, Irvine, Irvine, CA;

³Orthopedics, UC Irvine, Irvine, CA; ⁵Reeve-Irvine Res. Center, ⁴Univ. of California Irvine, Irvine, CA

Abstract: Peripheral nerve injuries (PNI), commonly resulting from trauma, repetitive motion or conditions like diabetes, can lead to muscle denervation. While nerve transfer surgery is key for successful muscle reinnervation, outcomes remain variable, especially at long post injury intervals. Despite this, our team has established that some patients experience substantial motor recovery with nerve repair surgery even months or years after PNI. Developing biomarkers to identify patients with a high probability of recovery could transform current surgical practice. This study demonstrates the feasibility of using spatial transcriptomics on human muscle biopsies to identify gene expression signatures that might be predictive of successful reinnervation. Under an IRB, patients consented to collection of small biopsy samples from upper extremity muscles including the trapezius and deltoid muscles. Biopsies were collected intra-operatively during standard of care Orthopaedic surgery. Here we report validation of workflow and preliminary findings through analysis of denervated deltoid muscle (confirmed pre-surgery EMG) and innervated trapezius collected from a patient undergoing reconstructive surgery 5 months following traumatic brachial plexus injury. Biopsy samples were flash-frozen in liquid nitrogen-cooled isopentane and processed using the high-resolution Visium HD 10X Genomics spatial transcriptomics platform. Valid barcode rates were 90% (control) and 91.2% (denervated), with over 98% of reads mapping confidently in both (98.2% for control and 98.3% for denervated). At 8 μ m bin size, the control sample averaged 99.6 UMIs and 71.9 genes per bin, while the denervated sample averaged 173.2 UMIs and 125.8 genes. These quality control metrics indicate the feasibility of using spatial transcriptomics to identify a unique gene expression signature in human muscle biopsies. Preliminary analyses revealed distinct gene expression profiles between samples. For instance, the acetylcholine receptor subunit gene

(CHRNA1) is markedly upregulated and diffusely expressed throughout myofibers in denervated muscle, whereas levels are much lower and signals are highly clustered in control muscle. Genes involved in neuromuscular junction formation, degeneration, and regeneration also show differential expressions. Together, these findings support the feasibility of spatial transcriptomics in human muscle biopsies and lay the groundwork for identifying gene expression signatures predictive of successful reinnervation. This could lead to improved diagnostic tools and therapeutic strategies in nerve repair and targeted regenerative medicine.

Disclosures: P.S. Pirbhoy: None. V. Murugan: None. C. Lee: None. R. Gupta: 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

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.07/O2

Topic: F.09. Motor Neurons and Muscle

Support: NIH grants 5RO111057704
NIH grants 15377331(P41)
Stratton VA Medical Center of the Department of Veterans Affairs

Title: Electrocortical stimulation of sensorimotor cortex (SMC) changes glutamatergic and neurotrophic function and related gene expression in rat spinal cord

Authors: *Y. WANG¹, B. HERRON², Y. CHEN¹, X. Y. CHEN¹, J. S. CARP¹, J. R. WOLPAW^{1,2};

¹Natl. Ctr. for Adaptive Neurotechnologies, Albany Stratton VA Med. Ctr., Albany, NY; ²State Univ. of New York, Univ. of Albany, Albany, NY

Abstract: Weak electrocortical stimulation (ECS) of rat sensorimotor cortex (SMC) for 30 days has short-term and long-term effects on spinal cord reflexes and GABAergic function. To further explore ECS effects on the spinal cord and their potential therapeutic uses, we studied ECS effects on glutamatergic and neurotrophic function and related gene expression. At the end of ECS, spinal motoneurons showed significant increases in: VgluT2 terminal number and NMDA and phosphor-AMPA glutamate receptors, phosphor-MAPK/ERKs, the synaptic vesicle protein synaptotagmin1, and TrkB and TrkC receptors and their mRNA for neurotrophic factors BDNF and NT3. Lamina 6-7 excitatory interneurons showed significant increases for AMPA receptor subunit 2 and the mRNA, synaptotagmin1 and the mRNA, and phosphor-TrkB and the mRNA. ECS-induced soleus H-reflex increase was positively correlated with both VgluT2 terminal

number increase and Trkc mRNA puncta increase of soleus motoneuron. These results provide new insight into the complex effects of ECS SMC on spinal cord motoneurons and lamina 6-7 interneurons and reveal the role of neurotrophic factors in these effects. The multiple effects described here are likely to strengthen supraspinal control of spinal cord function. Thus, they encourage and guide concurrent studies examining the capacity of ECS to improve functional recovery after spinal cord injury or other damage impairs supraspinal control.

Disclosures: Y. Wang: None. B. Herron: None. Y. Chen: None. X.Y. Chen: None. J.S. Carp: None. J.R. Wolpaw: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.08/O3

Topic: F.09. Motor Neurons and Muscle

Support: Internal grant Ariel University

Title: Action Observation in Healthy Adults: Effector-Independent Motor Gains and Cognitive Contributions

Authors: *S. FRENKEL-TOLEDO, G. SCHWELL;
Ariel Univ., Ariel, Israel

Abstract: Studies examining the effects of action observation (AO) on ipsilateral versus contralateral upper limb (UL) motor performance have reported mixed findings. Furthermore, the extent to which the cognitive component of sequence observation contributes to AO-related improvements in motor sequence execution remains unclear. This study investigated whether observing unilateral reaching movement (RM) sequences influences motor performance in an effector-dependent or effector-independent manner, and explored the role of cognitive sequence learning in this process. Sixty healthy right-handed adults were randomly assigned to one of three single-session intervention groups: (1) AO group - observed a left UL performing a sequential RM task; (2) Sequence Observation (SO) group - observed the same light-switch sequence without visible limb movement; or (3) Nature Observation (NO) group - viewed nature scenes. All participants performed a memorized RM sequence with both ULs (ipsilateral and contralateral to the observed limb) before, immediately after, and 24 hours following the intervention. In the AO group, a significantly greater reduction in reaching response time across both ULs was observed from pretest to posttest compared to the SO and NO groups. Additionally, performance gains in the AO group were similar for both ULs across all time points, indicating effector-independent improvement. In contrast, the SO group exhibited asymmetric gains, with a greater reduction in response time for the right UL from pretest to posttest and for the left UL from posttest to retest. Observing a unilateral UL reaching sequence

can enhance motor performance in both ULs, surpassing the effects of cognitive sequence observation alone. The findings suggest the involvement of motor effector-independent mechanisms and cognitive contributions in AO-driven motor gains.

Disclosures: S. Frenkel-Toledo: None. G. schwell: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.09/O4

Topic: F.09. Motor Neurons and Muscle

Title: Corticomuscular coherence of agonist and antagonist thigh musculature during graded-intensity isometric knee contractions

Authors: *M. KOOHESTANI¹, D. SHERMAN³, M. CHAPUT², M. STOCK¹, G. NORTE¹;
¹Univ. of Central Florida, Orlando, FL; ²Physical Therapy, Univ. of Central Florida, Oviedo, FL;
³Northeastern Univ., Boston, MA

Abstract: The motor cortex regulates the coordination of agonist and antagonist muscle activity, which is essential for joint stability and force control. Corticomuscular coherence (CMC) is a functional measure of connectivity between the motor cortex and muscles. Yet, it is unclear how CMC varies across function-specific frequency bands and contraction intensities, limiting our understanding of the neural mechanisms that govern joint stability and force modulation. We aimed to investigate how CMC is modulated across graded intensity isometric knee contractions, and to examine its relationship with muscle co-activation and force control. Twenty uninjured, physically active individuals (10 females, 21.9±2.5 years) performed isometric knee extension and flexion against an electromechanical dynamometer with their dominant leg at 30%, 50%, and 70% of their maximal voluntary isometric contraction (MVIC) force.

Electroencephalography (EEG) and electromyography (EMG) were recorded concurrently to assess CMC (alpha, beta, gamma), EEG power (central, motor), muscle activity, and antagonist-agonist muscle co-activation. Force control was evaluated using the coefficient of variation (CoV) and root mean square error (RMSE). Repeated-measures ANCOVAs were used to compare outcomes by contraction intensity (30%, 50%, 70%) and mode (agonist, antagonist), while controlling for sex. Knee extensor CMC did not differ by contraction intensity or mode. Knee flexor gamma-CMC was lower ($p=.044$, $d=-0.36$ [-0.67, -0.05]), and central gamma power was greater ($p=.005$, $d=0.29$ [-0.15, 0.72]), at 70% than 30% MVIC. Antagonist-agonist co-activation decreased with contraction intensity, while EMG amplitudes increased, regardless of contraction mode ($p=.001-.012$). Force steadiness (CoV) and accuracy (RMSE) decreased at higher intensity knee flexion (30% > 70% MVIC, $p=.014-.024$), but not during knee extension. Higher knee extensor beta-CMC associated with higher EMG co-activation ($r=0.598$, $p=.005$) and lower RMSE ($r=-0.484$, $p=.031$) at 50% MVIC. During high intensity knee flexion,

increased central gamma power paradoxically coincided with reduced gamma-CMC and degraded force control, suggesting that cortical commands become less effectively transmitted to muscles, and potentially compensated by subcortical circuits. The positive association between beta-CMC and both muscle co-activation and force accuracy is consistent with prior findings that beta-band coherence is a key neural signature of stable motor output. This intensity-dependent transition from cortical to subcortical control may provide a target for therapeutic interventions in motor disorders.

Disclosures: **M. Koohestani:** None. **D. Sherman:** None. **M. Chaput:** None. **M. Stock:** None. **G. Norte:** None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.10/O5

Topic: F.09. Motor Neurons and Muscle

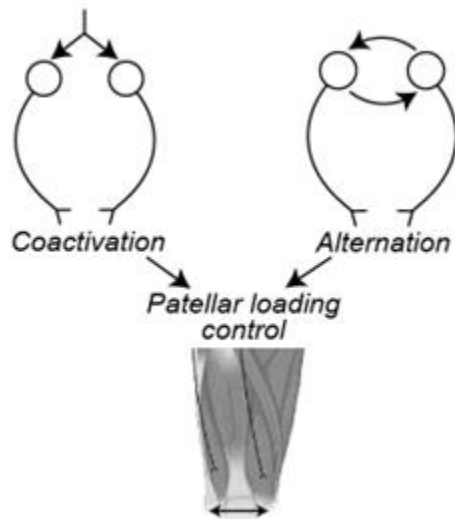
Title: Insufficient quadriceps synergy during fatigue in chronic patellofemoral injury

Authors: ***Z. WANG**¹, L. GRIFFIN²;

¹Washington State Univ., Pullman, WA; ²Univ. of Texas at Austin, Austin, TX

Abstract: Chronic patellofemoral injury is caused by the elevated patellofemoral joint loading and cartilage breakdown. Synergistic quadriceps activations are necessary to regulate normal joint loading, and fatigue can interfere with quadriceps synergistic control. **We investigated if quadriceps synergistic patterns change with fatigue and their implications in chronic patellofemoral injury.** 23 Individuals with chronic patellofemoral pain and 23 asymptomatic controls were recruited to perform sustained isometric knee extension until fatigue limits. We recorded surface EMG from vastus medialis oblique (VMO), vastus lateralis (VL) and rectus femoris (RF), which directly control patellofemoral joint. We characterized the quadricep synergy strength by quantifying the intermuscular EMG correlation using a small rolling window ($w = 200$ ms). We then analyzed the shift of quadricep synergistic patterns as fatigue progress between injury and non-injury groups. We found the three synergists exhibited coactivation (correlation > 0) and alternation (correlation < 0) patterns in both groups. In the non-injury group, the quadricep coactivation increases with fatigue (post-fatigue compared to pre-fatigue level: $167 \pm 37\%$, $152 \pm 62\%$, $151 \pm 54\%$, VMO-VL, VMO-RF, VL-RF, respectively), and alternation decreases with fatigue ($37 \pm 23\%$, $64 \pm 31\%$, $66 \pm 33\%$). However, significantly less increases with fatigue in coactivation ($125 \pm 21\%$, $112 \pm 22\%$, $108 \pm 24\%$) and less decreases with fatigue in alternation ($64 \pm 26\%$, $95 \pm 30\%$, $98 \pm 45\%$) were seen in the patellofemoral injury group. **The quadriceps coactivation and alternation may reflect the rivaling modulation between common neural drive and reciprocal inhibition among functionally connected quadriceps motor pools.** The less increases and decreases of common neural drive

and reciprocal inhibition in individuals with patellofemoral injury during fatigue may lead to patellar instability and increased loading. Those results indicated that the neuroplastic changes during fatigue can interfere with the neural control of the joint mechanics.



Disclosures: Z. Wang: None. L. Griffin: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.11/O6

Topic: F.09. Motor Neurons and Muscle

Title: Beyond the Primary Motor Response: Understanding the Elusive Secondary Motor Response to Transcranial Magnetic Stimulation

Authors: P. ROTELLI¹, *S. CHAUDHURY², J. CAIN³, E. BLACKWOOD⁴, W. FENG⁴, C. D. MACKINNON⁵, A. V. PETERCHEV⁴, A. HADJIPAPAS¹, C. C. CHARALAMBOUS⁴;

¹Univ. of Nicosia Med. Sch., Nicosia, Cyprus; ²King's Col. London, London, United Kingdom;

³Univ. of North Carolina, Chapel Hill, NC; ⁴Duke Univ., Durham, NC; ⁵Univ. of Minnesota, Minneapolis, MN

Abstract: Transcranial magnetic stimulation over the contralateral cortex elicits a short latency primary motor response, reflecting the functional integrity and excitability of the corticomotoneuronal pathways. In some muscles, transcranial magnetic stimulation also produces a long latency "secondary motor response" (SMR); however, the neural origin and function of the SMR is poorly understood. Here, we synthesize and critically evaluate the existing evidence from empirical studies that have reported SMRs. We systematically searched

relevant studies (1985-2025) in 5 databases using specific terms (e.g., transcranial magnetic stimulation, secondary response, etc.). After identifying 3492 and screening 2057 studies, respectively, we included 22 eligible studies (1990-2021) that reported SMR in neurotypical (19/22; N: 5-50; age: 3-64) and clinical (7/22; N: 1-28; age: 19-87) cohorts. All studies applied TMS over the motor cortex (22/22) adjacent to vertex using circular (8/22), figure-of-8 (1/22), or double cone (9/22) coils without neuronavigation (21/22). Most studies (19/22) demonstrated SMR elicitation on lower extremity muscles, mainly in the distal leg (dorsiflexors: 8/22; plantarflexors: 12/22). Reports of SMR in upper extremity (6/22) and facial (1/22) muscles were less common. SMR latencies ranged from 69-260, 20-400, and 28-31 millisecond for lower extremity (e.g., dorsiflexors, plantarflexors, etc.), upper extremity (e.g., wrist flexors and extensors, etc.), and facial (inferior orbicularis oculi) muscles, respectively. In both upper and lower extremity muscles, SMR latency was shorter in flexors than in extensors. Diseases of the central nervous system (e.g., stroke, spinal cord injury, Parkinson's, cerebellar ataxia, etc.) lead to lower SMR response rate and delayed latency. Furthermore, SMR elicitation depends on four methodological factors: 1) voluntary pre-activation of the antagonist muscle group, 2) postural manipulation, 3) joint immobilization, and 4) foot position. Several neural origins of SMR are proposed: 1) segmental stretch reflex, 2) long-loop reflex, 3) polysynaptic neural network circuit related to postural adjustment in the brainstem, 4) spindles activated by γ -motoneuron activity, and 5) startle reflex. In conclusion, our findings demonstrate that the SMR can be elicited mainly in lower extremities and are modulated by specific methodological and physiological factors. Both peripheral and central neural substrates are likely to contribute to the generation of the SMR. Further investigation is warranted to elucidate the full extent of the neural origins and function of SMR.

Disclosures: P. Rotelli: None. S. Chaudhury: None. J. Cain: None. E. Blackwood: None. W. Feng: None. C.D. MacKinnon: None. A.V. Peterchev: None. A. Hadjipapas: None. C.C. Charalambous: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.12/O7

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant SC3GM139683

Title: Upper limb nerve conduction study before and after heavy backpack carriage

Authors: J. HEIN¹, K. SAUL², *D. J. SCHMIDT¹;

¹Kinesiology, California State Univ. San Marcos, San Marcos, CA; ²Mechanical and Aerospace Engin., North Carolina State Univ., Raleigh, NC

Abstract: People who carry heavy backpacks can experience symptoms of upper limb nerve compression such as pain, tingling, and muscle weakness. Repeated heavy backpack carry has been linked to backpack palsy from traction injury to the brachial plexus. Incidence rate of backpack palsy is 5.6 cases per 10,000 military recruits. Backpack palsy can result in prolonged lack of sensation and muscle weakness in the arms and hands. The aim of our study was to determine if short-term effects on upper limb nerve conduction are present after a single session of backpack carriage. Our overarching goal is to understand both the short-term and long-term effects of backpack carry on nerve compression, risk factors for backpack palsy, and use of the hands for those who carry backpacks for occupations including military and wildland firefighters. Twenty-eight participants including 18 females (24 ± 4 yrs, 68.02 ± 15.04 kg, 164.5 ± 6.7 cm) and 10 males (28 ± 9 yrs, 82.14 ± 7.78 kg, 178.9 ± 3.9 cm) were recruited as a convenience sample. Participants completed 40 min of treadmill walking while carrying a properly fitted military-style large frame backpack with hip belt loaded to 30% bodyweight. Nerve conduction study (NCS) was completed on the median nerve of the dominant arm. Motor nerve amplitude of the action potential was measured for stimulation at the wrist, elbow, and axilla. Supramaximal stimulation was completed with active recording from the abductor pollicis brevis (motor) or index finger (sensory). NCS was completed before (PRE), after walking with backpack (POST), and after a 15-min seated recovery (REC). Results indicated a significant decrease in motor nerve action potential PRE to POST backpack carriage for stimulation at the elbow and at the axilla ($p < 0.001$). Motor nerve action potential amplitude demonstrated a mean of 11.50 ± 3.36 μ V at PRE, 10.10 ± 3.10 μ V at POST, and 10.48 ± 3.36 μ V at REC with stimulation at the elbow. With stimulation at the axilla, action potential amplitude was a mean of 12.22 ± 3.22 μ V at PRE, 10.54 ± 3.43 μ V at POST, and 11.18 ± 3.11 μ V at REC. For axilla stimulation, the action potential amplitude at REC was significantly different from PRE ($p = 0.003$) and POST ($p = 0.037$) timepoint measurements demonstrating that the 15-min seated rest resulted in increase in motor nerve conduction, but not to the PRE level. Sensory peak-to-peak action potential amplitude also decreased significantly from PRE to POST ($p < 0.001$). Our findings reveal that 40 min of walking with a heavy backpack resulted in significant decrease in motor and sensory nerve conduction demonstrating a short-term effect on the upper limb that could potentially impact use of the arms or hands after backpack carry.

Disclosures: J. Hein: None. K. Saul: None. D.J. Schmidt: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.13/O8

Topic: F.09. Motor Neurons and Muscle

Title: Rhabdomyolysis Following Elective Craniotomy: A Prospective Observational Study

Authors: *S. DUBE, A. BINDRA, A. SURI, S. BAGCHI, A. CHATURVEDI;
AIIMS, New Delhi, India

Abstract: Background: Rhabdomyolysis is a condition characterized by muscle tissue destruction with subsequent release of damaged muscle cell products into the circulation leading to various systemic effects. There are several reports of rhabdomyolysis after bariatric, urologic and gynaecologic surgery, but same has not been studied much in neurosurgical patients. We aimed at studying rhabdomyolysis (measured in terms of elevation of muscle enzyme) in elective craniotomy patients. **Methodology:** After ethics committee approval ASA, I/II patients of 18-60 years undergoing elective craniotomy were enrolled. In all patients apart from routine investigations, serum creatinine kinase (CK) and myoglobin were measured preoperatively, immediate post operatively and then daily for 3days. Renal injury was assessed with daily AKIN scoring and serum NGAL levels. The total duration of ICU/hospital stay, post operative complications and neurological outcome at discharge were noted. **Results:** A total of 82 patients were enrolled. We observed a significant rise of CK and myoglobin levels from the baseline values at all time intervals [Highest CK rise at 1st post operative day, Median 195.2 IU/L(IQR;95-260.7) and highest myoglobin rise immediately after surgery 258.9 ng/ml (IQR 75.6-222.7 ng/ml)]. The independent risk factors for peak elevation of CK and MG were lateral surgical position (OR 2.3) and surgical duration of more than 300 minutes (OR 1.9). In our study NGAL levels were higher on the first postoperative day which normalized over next 2 days and 3 patients had some degrees of renal injury. **Conclusion:** Significant CK and myoglobin elevation occurs after elective craniotomy surgery. Lateral surgical positioning and surgical duration of more than 300 minutes are the independent risk factors for CK and myoglobin elevation following elective neurosurgery.

Disclosures: S. Dube: None. A. Bindra: None. A. Suri: None. S. Bagchi: None. A. Chaturvedi: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.14/O9

Topic: F.09. Motor Neurons and Muscle

Support: AG44615
HL146114

Title: Bdnf/trkb.fl signaling promotes mitochondrial biogenesis in cervical ventral horn

Authors: *D. DASGUPTA¹, A. DAVIS¹, G. HERNANDEZ VIZCARRONDO¹, J. DAVIS¹, M. J. FOGARTY², C. B. MANTILLA³, G. C. SIECK⁴;

²Dept. of Physiol. & Biomed. Engin., ¹Mayo Clin., Rochester, MN; ³Mayo Clin., Rochester, MN, ; ⁴Physiol. & Biomed. Engin., Mayo Clin., Rochester, MN

Abstract: Brain derived neurotrophic factor (BDNF) signals through its high-affinity full-length tropomyosin receptor kinase-B (TrkB.FL). Previously, we showed that BDNF/TrkB.FL signaling activates pCREB^{S133} phosphorylation and its nuclear translocation in phrenic motor neurons (PhMNs) in rats. In other tissue, pCREB^{S133} transcriptionally activates PGC1 α with a downstream increase in TFAM expression thereby promoting mitochondrial biogenesis. In the present study, we used a novel chemogenetic rat model (*TrkB^{F616A}*) with a knock-in allele sensitive to the selective kinase inhibitor 1NMPP1 to inhibit TrkB.FL kinase activity. We hypothesized that 1NMPP1-induced inhibition of TrkB.FL kinase reduces BDNF-induced pCREB^{S133} phosphorylation and downstream expression of PGC1 α and TFAM leading to reduced mitochondrial biogenesis. Female (n=3 in each group) and male (n=3 in each group) wildtype Sprague-Dawley rats were treated intrathecally at C₄ with either artificial cerebrospinal fluid (aCSF) or BDNF (4 ng/ 300 g body weight; diluted in aCSF) for 40 mins, to demonstrate the effect of increased BDNF on the pCREB^{S133}/PGC1 α /TFAM signaling cascade in cervical ventral horn. Another set of female (n=3 in each group) and male (n=4 in each group) *TrkB^{F616A}* rats were treated for 2 h with 1NMPP1 (25 μ M; dissolved in DMSO and diluted in saline) or the vehicle DMSO (equal volume as 1NMPP1; diluted in saline) administered intraperitoneally. After 2 h, both groups were treated intrathecally at C₄ with BDNF (4 ng/ 300 g body weight; diluted in aCSF) for 40 min. Acute intrathecal BDNF increased the pTrkB.FL^{Y817} autophosphorylation with a downstream phosphorylation of pCREB^{S133}, that further promotes transcriptional activation of PGC1 α and TFAM signaling cascade, with an associated increase in mitochondrial DNA (mtDNA) copy number as compared to aCSF treated controls. 1NMPP1 treatment blunted BDNF-induced pTrkB.FL^{Y817} phosphorylation and downstream activation of the pCREB^{S133}/PGC1 α /TFAM signaling cascade. 1NMPP1 treatment resulted into reduction of mtDNA copy number compared to vehicle treated controls. We conclude that 1NMPP1 mediated inhibition of BDNF/TrkB.FL signaling inhibits mitochondrial biogenesis in rat cervical ventral horn.

Disclosures: D. Dasgupta: None. A. Davis: None. G. Hernandez Vizcarrondo: None. J. Davis: None. M.J. Fogarty: None. C.B. Mantilla: None. G.C. Sieck: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.15/O10

Topic: F.09. Motor Neurons and Muscle

Support: NIA/NIH 1R01AG067758

Title: Longitudinal assessment of neuromuscular deficits in young and aged mice following CTB-Saporin induced motor neuron injury

Authors: *F. B. DARVISHI¹, A. ROSHANI DASHTMIAN², W. ARNOLD³, M. WANG⁴;

¹NextGen precision health, Columbia, MO; ³NextGen Precision Hlth., ²Univ. of Missouri, Columbia, Columbia, MO; ⁴Univ. of Missouri, COLUMBIA, MO, MO

Abstract: Motor neurons (MNs) are essential for voluntary movement, forming the final connection between the spinal cord and muscle. Their loss, due to aging or disease, leads to motor unit (MU) disruption, denervation, and functional decline. While surviving MNs may compensate through collateral sprouting, this ability diminishes with age. To investigate how aging affects MN loss and compensation, we used intramuscular injection of cholera toxin B-subunit conjugated to saporin (CTB-sap), a targeted model of MN ablation via retrograde transport. Although this model has been used to induce MN degeneration, its functional impact across time and age remains poorly defined. Our study aimed to characterize longitudinal changes in MU function after CTB-sap injury and determine whether aging limits neuromuscular compensation. Young (8-10 months) and old (26-28 months) C57BL/6 mice (n=10 per group) underwent baseline assessments of motor unit and muscle function, including compound muscle action potential (CMAP), motor unit number estimation (MUNE), repetitive nerve stimulation (RNS), in vivo twitch and tetanic torque, and hindlimb grip strength. CTB-sap was then unilaterally injected into the right gastrocnemius to induce selective spinal MN ablation, followed by repeated functional assessments over 13 weeks. Injured and uninjured limbs were compared at the endpoint to evaluate age-related deficits. Both age groups exhibited rapid, sustained reductions in CMAP and MUNE beginning one week after injury and persisting through all-time points. Muscle torque and grip strength were also significantly reduced throughout the study. At the endpoint, injured limbs in both groups showed lasting impairments in CMAP, MUNE, tetanic torque, and grip strength compared to contralateral limbs. Notably, old mice exhibited greater CMAP decrement during RNS, indicating impaired synaptic transmission with aging. Our findings demonstrate that the CTB-sap model is well-suited for investigating neuromuscular deficits and compensatory mechanisms in both young and aged mice. Its ability to induce sustained motor unit and muscle impairments across ages supports its broad applicability for experimental studies of motor neuron loss. Importantly, the pronounced deficits in synaptic transmission observed in aged mice highlight the value of this model for exploring age-related vulnerabilities and for developing targeted interventions to preserve motor function in older populations.

Disclosures: F. B. Darvishi: None. A. Roshani Dashtmian: None. W. Arnold: None. M. Wang: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.16/O11

Topic: F.09. Motor Neurons and Muscle

Title: Sex and Muscle Specific Neuromuscular Response to Short-Term Moderate-Intensity Exercise

Authors: *A. B. GALENTINE, C. FIGUEROA, J. M. SPITSBERGEN;
Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Exercise duration is a critical factor in the modulation of neuromuscular plasticity. Our goal is to determine the minimum duration of moderate-intensity treadmill running necessary to impact neuromuscular plasticity. We hypothesize that 5 days of moderate-intensity exercise will increase muscle fiber area and glial cell line-derived neurotrophic factor (GDNF) protein and mRNA expression in recruited muscles. Following treadmill familiarization, male and female rats were randomly assigned to a sedentary or exercise group and began the training at 8 weeks old (n=6). Exercise consisted of a 10-minute warmup (33-40% maximal aerobic speed [MAS]), 50-minute training (55-65% MAS), and 3-minute recovery (23-30% MAS) for 5 days. Soleus (slow-twitch) and plantaris (fast-twitch) hindlimb muscles were harvested 24 hours after the last exercise bout. Tissues were processed for protein and mRNA quantification by ELISA and RT-qPCR respectively and morphological measurements by immunohistochemical staining. Data is reported as the mean $\pm$ standard error of the mean and analyzed by two-way analysis of variance. Tukey's post hoc analysis was used to assess significance among groups ($p \leq 0.05$). We found that 5 days of exercise was sufficient to increase the cross-sectional area of type I ($1612.64 \pm 604.27 \mu\text{m}^2$ vs $956.92 \pm 209.09 \mu\text{m}^2$) and type IIa ($1644.36 \pm 339.69 \mu\text{m}^2$ vs $1019.15 \pm 174.57 \mu\text{m}^2$) muscle fibers in male plantaris with exercise. No change was observed in the type IIb fibers. GDNF protein content increased in males in soleus and plantaris respectively ($1.67 \pm 0.18 \text{ pg/mg}$ vs $0.43 \pm 0.06 \text{ pg/mg}$ and $2.12 \pm 0.51 \text{ pg/mg}$ vs $0.62 \pm 0.17 \text{ pg/mg}$). Exercise showed no effect on GDNF protein expression in females, though expression in soleus exceeded that of plantaris in control ($0.62 \pm 0.15 \text{ pg/mg}$ vs $0.33 \pm 0.07 \text{ pg/mg}$) and exercise ($0.69 \pm 0.18 \text{ pg/mg}$ vs $0.24 \pm 0.03 \text{ pg/mg}$) groups. There was no difference in GDNF protein levels between the muscle types in males. GDNF mRNA expression in soleus was upregulated (1.70-fold) with exercise in males. These findings suggest that the timing of the neuromuscular response may differ in males and females with males exhibiting greater GDNF expression than females after 5 days of exercise. Females typically have a higher composition of slow-twitch muscle fibers which may explain the greater GDNF protein content in soleus. As this study is continued, we will examine the morphological changes in the neuromuscular junction and alpha motor neuron cell bodies. Understanding the impact of exercise duration on neuromuscular plasticity in both sexes and different muscle types is critical in the development of more accurate exercise regimen prescriptions.

Disclosures: A.B. Galentine: None. C. Figueroa: None. J.M. Spitsbergen: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.17/O12

Topic: F.09. Motor Neurons and Muscle

Support: NIH R29 NS31857
NIH 5U54MD013376
NIH 5UL1GM11897
NIH AI174952
NNSA PATH

Title: Cxcr4 mediated gp120 interaction in the caudate and putamen of the hiv-1 transgenic rat as a contributor to motor impairment

Authors: *M. D. WORTHINGTON¹, S. WILLIAMS³, J. BRYANT⁴, L. EDELSTEIN⁵, F. J. DENARO²;

²Biol., ¹Morgan State Univ., Baltimore, MD; ³Univ. of Maryland, Sch. of Medicine, IHV, Baltimore, MD; ⁴Univ. of Maryland, Baltimore, MD; ⁵Medimark Corp., San Diego, CA.

Abstract: HIV infections continue to be newly diagnosed globally. While treatments have markedly improved, there is no cure. Studies of patients both on antivirals and untreated have demonstrated HIV's affinity to the nervous system. In fact, the brain has been noted as an important HIV reservoir. Patients on antiviral therapy still harbor virus in the brain. As a result, HIV central nervous system disease has become an important noninfectious comorbidity. Individuals living with HIV must be on the antivirals for the rest of their life to maintain their health. Even so as time passes neurologic symptoms begin to emerge. The mechanism of this viral pathology has not been well elucidated. Uncovering the pathways of neuronal death and dysfunction could help develop adjunct therapies for the brain. We have been using our model of the HIV-1 transgenic rat (HIV-1 TGR) to study the chronic long-term effects of HIV infection. This model has transgenes for gp120, tat and nef, and we previously detected these molecules by ELISA and immunocytochemistry in this model. Proteins tat and nef do not need a receptor for cellular entry so their effects can be generalized. Alternatively, gp120 has been shown to bind to the CXCR4 receptor in humans and in this rat model. Microscopic analysis of the TGR brain has suggested a level of selective neuronal vulnerability in this model. In particular, the dopaminergic system seems to be markedly affected. One hypothesis for this observation is the distribution of the CXCR4 receptors in a particular part of the brain which can cause dysfunction in that area as bound gp120 is toxic to the cells. We previously noted degeneration of the dopaminergic projections to the caudate. In the present study we continued our analysis finding CXCR4 receptors by immunocytochemical staining on glia cells in caudate/putamen together with markers for free radical stress. It is hypothesized that this may cause disruption of the supportive glia cells of the dopaminergic axons which in turn would contribute to axonal degeneration. These findings may help to develop this model for the identification of neuroprotectants.

Disclosures: M.D. Worthington: None. S. Williams: None. J. Bryant: None. F.J. Denaro: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.18/O13

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant AG044615
NIH Grant AG057052
NIH Grant HL146114
Mayo Clinic

Title: Differences in TrkB mRNA density in adult rat phrenic motor neurons

Authors: R. C. MARTINEZ, S. RANA, H. M. GRANSEE, W.-Z. ZHAN, G. C. SIECK, *C. B. MANTILLA;
Mayo Clin., Rochester, MN

Abstract: Motor neuron plasticity and survival depend on several trophic factors including signaling via the tropomyosin receptor kinase B (TrkB) receptor. Differences in motor neuron properties across motor units may also reflect differential trophic influences, but molecular factors are not available to specifically identify motor unit populations and comparisons across muscles of predominant muscle fiber type composition are inadequate to address this question. Leveraging the extensive characterization of phrenic motor neurons (PhMN) it is possible to use motor neuron size (i.e., somal surface area) to indicate motor unit type (lower force slow-twitch, fatigue resistant units comprising smaller motor neurons vs. higher force fast-twitch fatigable units comprising larger motor neurons). To examine whether TrkB expression reflects these size-related properties, we quantified TrkB mRNA in five adult male Sprague-Dawley rats. PhMNs were retrogradely labeled by intrapleural injection of Alexa Fluor 488-conjugated cholera-toxin subunit B. Cervical C3-C5 cryosections (10 μm) were processed with multiplex RNAscope, and confocal z-stacks were analyzed using NIS-Elements to identify labeled PhMN, determine their size and segment nuclear and cytoplasmic regions to compute TrkB mRNA transcript density (transcripts/volume). A total of 287 PhMNs were studied and the expected range of PhMN size was observed. Significant differences in PhMN somal surface area were observed, with significant differences across animals (means 3500 to 5500 μm^2 ; $p < 0.001$). PhMNs were classified into tertiles according to size for each animal. On average, individual PhMNs contained 470 ± 230 TrkB mRNA transcripts, with between-animal variation ($p < 0.001$). Accordingly, transcript density data were analyzed using a mixed linear model with animal as a random effect. A strong negative association between PhMN somal surface area and total TrkB mRNA density was observed ($r^2 = 0.3$; $p < 0.001$). Larger PhMNs expressed a greater number of TrkB mRNA transcripts overall but fewer per unit volume (lower transcript density). Cellular compartment analysis showed that nuclear TrkB mRNA density was size-invariant, whereas cytoplasmic density declined by $\sim 40\%$ from the smallest to the largest PhMN tertile. Thus, lower force motor units preserve a higher cytosolic TrkB mRNA density, which may contribute to higher TrkB receptor translation. These findings establish a baseline for TrkB-related

neurotrophic signaling and underscore the importance of motor unit identity and subcellular compartmentalization as key factors in interpreting motor plasticity.

Disclosures: R.C. Martinez: None. S. Rana: None. H.M. Gransee: None. W. Zhan: None. G.C. Sieck: None. C.B. Mantilla: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.19/O14

Topic: F.09. Motor Neurons and Muscle

Support: AHA Grant 25CDA1445873

Title: Mapping Vestibular-Evoked Myogenic Potentials in Upper Limb Muscles

Authors: *I. NOVOA CORNEJO¹, C. CUADRA²;

¹SUNY at Buffalo, Buffalo, NY; ²Rehabil. Sci., State Univ. New York at Buffalo, Buffalo, NY

Abstract: Vestibular inputs are known to modulate muscle activity for postural control, yet their influence on upper limb (UL) motor coordination remains underexplored. This is particularly relevant in the context of post-stroke motor impairments, where abnormal muscle activation is often associated with disinhibition of bulbospinal pathways, including the reticulospinal and rubrospinal tracts. However, emerging evidence implicates the vestibulospinal tract in mediating asymmetric and abnormal muscle activation patterns, especially in the spastic muscles of stroke survivors. Despite its known projections to cervical motoneurons, the contribution of vestibular-evoked myogenic potentials (VEMP) to UL muscle activity is poorly characterized in both healthy and clinical populations. We aimed to map VEMP responses in UL muscles of able individuals to establish normative patterns of UL vestibulospinal connectivity. Eleven subjects stood with one arm raised, holding a 0.5-1 kg weight in a clenched fist. EMG recording from anterior deltoid (DEL), biceps brachii (BB), and flexor carpi radialis (FCR) were collected. Additionally, the sternocleidomastoid (SCM) was included to confirm the integrity of the VEMP response. Visual feedback on FCR EMG guided participants to maintain consistent muscle activation and posture. VEMP stimulation consisted in a 500 Hz tone bursts, 4 ms duration at 120 dB, with a total trial duration of 300 ms. 200-300 VEMP trials were collected per arm. VEMP response latencies followed a clear proximal-to-distal pattern ($p < 0.05$): SCM (18.98 ± 2.92 ms), DEL (41 ± 9.6 ms), BB (51.28 ± 9.55 ms), and FCR (59.9 ± 12.12 ms). Peak-to-peak magnitude analysis using repeated measures ANOVA revealed that SCM showed significantly larger responses (19.19 ± 1.83 au) compared to UL muscles ($p < 0.05$). In contrast, DEL (11.98 ± 1.60 au), BB (12.78 ± 2.59 au), and FCR (12.36 ± 2.38 au) showed similar magnitudes, with no statistically significant differences among them. The likelihood of detecting significant responses in individual trials did not differ statistically among the UL muscles. These findings

demonstrate more consistent VEMP recruitment in proximal compared to distal UL muscles, following an anatomically predictable latency gradient. The results establish a normative baseline for interpreting the contributions of the vestibular system to motor impairment following stroke. They will inform future neuromodulatory interventions targeting vestibulospinal pathways in rehabilitation.

Disclosures: I. Novoa Cornejo: None. C. Cuadra: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.20/O15

Topic: F.09. Motor Neurons and Muscle

Support: DHA Restoral Funds

Title: Repeated Occupational Whole Body Vibration Exposures Cause Skeletal Muscle Weakness and Alterations in Muscle Spindle Structure.

Authors: *S. H. ROMER, D. R. MCMEANS, M. SONNER;
Naval Med. Res. Unit Dayton, Dayton, OH

Abstract: Musculoskeletal disorders (MSDs) are prevalent in occupations involving whole-body vibration (WBV). Rotary wing aircraft crew, in particular, have a heightened risk of developing MSD due to the unique operational environments of these aircraft which include repeated exposures to low-frequency WBV. Unlike therapeutic WBV protocols, occupational WBV exposures are typically longer, repeated, and occur at lower frequencies. This study aimed to evaluate the effects of repeated low-frequency WBV on neuromuscular structure and function. Adult male rats were exposed to three-dimensional WBV at 5 hertz for 2 hours per day, 5 days per week, over a 4-week period—mimicking the average frequency and duration of daily rotary-wing flight. Following the exposure period, *in vivo* assessments of hindlimb skeletal muscle contractile function were conducted, and muscles were harvested for post-hoc immunohistochemical analysis of neuromuscular junctions (NMJs) and muscle spindles. WBV-exposed rats demonstrated an 11% reduction in specific force during tetanic contraction compared to controls (Control: 1958.1 ± 35.3 mN/g; WBV: 1735.7 ± 58.3 mN/g; $n = 12$; $p = 0.028$). Similarly, the force-frequency relationship revealed a 12% decrease in maximal force-generating capacity in WBV-exposed animals (Control: 1985.1 ± 58.9 mN/g; WBV: 1744.7 ± 96.9 mN/g; $n = 12$; $p = 0.048$). While NMJ morphology remained unchanged, WBV exposure resulted in a 9% increase in the inter-rotational distance within muscle spindles (Control: 11.1 ± 0.2 μm , $n = 14$; WBV: 12.1 ± 0.4 μm , $n = 12$; $p = 0.042$), suggesting altered afferent axon terminal structure. These findings indicate that repeated exposure to occupationally relevant

WBV impairs skeletal muscle force generation and induces structural changes in proprioceptive sensory components, specifically the muscle spindle.

Disclosures: S.H. Romer: None. D.R. McMeans: None. M. Sonner: None.

Poster

PSTR028: Motor Neurons: Activity, Sensory, and Central Control: Exercise, Injury, and Disease

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR028.21/O16

Topic: F.09. Motor Neurons and Muscle

Support: SPO296125 UAPGT

Title: Upper motor circuitry myelin abnormalities in treated Spinal Muscular Atrophy

Authors: *L. KOEPKE¹, B. YALCIN², R. DREXLER², M. MONJE²;

¹Stanford Univ., Redwood City, CA; ²Neurol., Stanford Univ., Stanford, CA

Abstract: Introduction:

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder caused by SMN1 mutations, resulting in motor neuron loss and muscle atrophy. FDA-approved SMN-enhancing therapies improve outcomes, but motor deficits persist. Though SMA is often classified as a lower motor neuron disease, evidence suggests the entire motor circuit, including upper motor neurons and glial cells, plays a critical role. This study explores how brain-resident glia—microglia, astrocytes, and oligodendrocytes—contribute to SMA pathology, aiming to identify new therapeutic targets.

Methods:

We used the “delta 7” SMA mouse model and treated mice with two SMN-upregulating therapies to extend lifespan beyond the typical 14 days. Motor function was assessed in untreated and treated KO and wildtype littermates via surface righting and hindlimb suspension (pups) and running wheel (adults) behavioral assays. Brain tissue was analyzed using confocal microscopy for glial cell populations and electron microscopy for myelin ultrastructure.

Results:

Treated P10 KO pups show impaired righting and suspension performance. Treated 3-month-old SMA mice run shorter distances and have fewer newly generated oligodendroglial cells after motor skill learning. Treated adult SMA mice also exhibit reduced mature oligodendrocytes (but not OPCs) in key white matter regions and globally increased reactive microglia in the cingulum, corpus callosum, motor/somatosensory cortices, and dentate gyrus. Electron microscopy reveals thinner myelin sheaths on small-diameter axons in M2 motor cortex projections in the cingulum of the corpus callosum and altered myelinated axon density, indicating dysmyelination in mice with SMA following SMN-correcting therapies.

Conclusion:

Motor dysfunction persists despite SMN-restorative treatment and correlates with glial abnormalities. Altered oligodendrocyte and microglial populations in upper motor circuitry, along with dysmyelination, may contribute to residual motor deficits and offer new targets for adjunctive therapies in SMA.

Disclosures: L. Koepke: None. B. Yalcin: None. R. Drexler: None. M. Monje: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.01/P1

Topic: F.09. Motor Neurons and Muscle

Title: An In Vitro Model for Motor Neurons Displays Axonal and Mitochondrial Deficiencies Associated with Type 2A Charcot-Marie-Tooth Disease

Authors: M. MAGDESIAN¹, G. VIANA², R. DA SILVA³, L. KUYLTJES², A. JOHNSON⁴, K. XU⁵, H. RUETH⁴, M. L. HENDRICKSON⁴, M. SCHEIDELER⁶, K. FORSEY⁷, *S. LIN⁸;

¹Dept. of Physics, ²Ananda Devices, Saint-Laurent, QC, Canada; ³Montreal Neurolog. Inst., Montreal, QC, Canada; ⁴BrainXell, Madison, WI; ⁵BrainXell Inc., Madison, WI; ⁶HumanFirst Therapeut. LLC, Silver Spring, MD; ⁷Charcot-Marie-Tooth Assn. (CMTA), Glenolden, PA; ⁸Charcot-Marie-Tooth Assn., Glenolden, PA

Abstract: Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy that affects peripheral sensorimotor nerves, causing pain, muscle weakness and atrophy. CMT type 2A (CMT2A) is the most frequent subtype of axonal CMT and is considered one of the earlier onset forms of type 2 CMT. It is associated with mutations in Mitofusin 2 (MFN2), a GTPase anchored to mitochondrial membrane involved in equilibrium of mitochondrial fusion/fission. We investigated the impact of the MFN2 R364W mutation on aspects of neuronal cell morphology and mitochondria activity, using microfluidic plates containing compartments to accommodate neuronal elongation. iPSC-derived motor neurons were generated from a healthy human control line and a CMT2A patient-derived line with the MFN2 R364W mutation. Both populations of motor neurons were cultured on the microfluidic plates to organize neurons into standard reproducible networks with cell bodies positioned in one compartment and axons elongated to a second compartment. Consistent orientation of axons enabled automated imaging/assessment of seven neuromorphological factors (7NMP) including cell size, axonal length, neurite connections, as well as mitochondrial mobility and morphology using custom-created software. Standardization of neuronal network cultures and analysis with the platform supported the elucidation of key differences between CMT2A and healthy populations, including statistically significant changes in cell number and size plus mitochondrial movement. Non-statistically significant trends were observed for many other traits including axonal material, branching, number of branching junctions, axon breadth, and neurite straightness, as well as

average anterograde mitochondrial velocity and aspect ratio of upper chamber, neurite channel, and lower chamber mitochondria. Mouse models for CMT2A are limited and our study highlights the advantage of using human-derived in vitro models for faster and more effective disease modeling, rapid drug screening, and a deeper understanding of the mechanisms underlying this devastating disease that has a huge impact on children's development.

Disclosures: **M. Magdesian:** A. Employment/Salary (full or part-time): Ananda Devices. **G. Viana:** A. Employment/Salary (full or part-time): Ananda Devices. **R. Da Silva:** A. Employment/Salary (full or part-time): Ananda Devices. **L. Kuyltjes:** A. Employment/Salary (full or part-time): Ananda Devices. **A. Johnson:** A. Employment/Salary (full or part-time): BrainXell. **K. Xu:** A. Employment/Salary (full or part-time): BrainXell. **H. Rueth:** A. Employment/Salary (full or part-time): BrainXell. **M.L. Hendrickson:** A. Employment/Salary (full or part-time): BrainXell. **M. Scheideler:** F. Consulting Fees (e.g., advisory boards); Charcot-Marie-Tooth Association. **K. Forsey:** None. **S. Lin:** None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.02/P2

Topic: F.09. Motor Neurons and Muscle

Title: Reconstructing the functional topography of peripheral nerves for selective neurostimulation

Authors: ***L. TONI**¹, V. FOSSATI², C. VERARDO², S. MICERA³, S. ROMENI⁴;
¹Scuola Superiore Sant'Anna, Milano, Italy; ²Scuola Superiore Sant'Anna, Pisa, Italy; ³Swiss Federal Inst. of Technol., Lausanne, Switzerland; ⁴San Raffaele Hosp., Milano, Italy

Abstract: Recent advances in electrical stimulation of the median and radial nerves through implanted interfaces have demonstrated the potential to restore fine motor functions in individuals with upper limb paralysis. To successfully translate these promising demonstrations into clinical practice, developing fast and robust routines for determining stimulation protocols that selectively activate specific muscles will be important. While computational models allow large-scale testing of possible stimulation protocols, the development of personalized models that accurately represent the internal organization of implanted nerves remains relatively unexplored. To achieve selective activation, a key factor will likely be the characterization of the association between nerve fibers within a nerve cross-section and the muscles they innervate, the so-called nerve "functional topography". A promising hypothesis suggests that a nerve's functional topography may be reconstructed from calibration data obtained directly from the implanted interface, eliminating the need for precise knowledge of its internal geometrical structure. Here, we present a computational framework to reconstruct the functional topography of a simulated human median nerve using recruitment curves that represent muscle-specific responses to

monopolar stimulation protocols. Our approach relies on a surrogate nerve cross-section composed of circular fascicles, with their number and radii sampled from statistical distributions reported in the literature for the human median nerve. To localize the fibers innervating each muscle within the surrogate nerve, we iteratively selected circular clusters of fibers until the resulting recruitment curves matched those observed in the target nerve. Despite structural differences between the surrogate and target nerves, the fibers associated with each muscle consistently occupied similar regions within the nerve cross-section. To assess the practical utility of the reconstructed topography, we optimized selective stimulation protocols on the surrogate nerve and then applied them to the target nerve, comparing the resulting selectivity. We found that the optimized protocols achieved both high selectivity and strong agreement in selectivity profiles between the surrogate and target nerves. These results suggest that computational models can be effectively used to design selective stimulation protocols without requiring subject-specific information about internal nerve organization.

Disclosures: L. Toni: None. V. Fossati: None. C. Verardo: None. S. Micera: None. S. Romeni: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.03/P3

Topic: F.09. Motor Neurons and Muscle

Title: A robust platform of human iPSC-derived motor neurons for ALS disease modelling and neurodegeneration-focused drug discovery

Authors: T. OOSTERVEEN¹, L. FOULSER¹, W. BERNARD¹, G. MASTROGIOVANNI¹, *T. BROWN¹, S. MILDE¹, K. FIRTH¹, O. DOVEY¹, B. NEWMAN¹, H. GARNETT¹, V. YIANNI¹, S. SALIC-HAINZL², S. BARBARIA²;

¹bit.bio, Cambridge, United Kingdom; ²bit.bio discovery, bit.bio, Vienna, Austria

Abstract: The lower motor neurons are a diverse group of neuronal subtypes that regulate muscle and glandular activity. They form complex neural circuits by integrating inputs from interneurons, sensory neurons, and upper motor neurons to control behaviours such as locomotion. Disruption of these networks leads to motor neuron diseases (MNDs), including spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). Therapeutic development for MNDs is limited by the poor translational relevance of animal models and the lack of scalable, consistent in vitro systems. Although human iPSCs offer a renewable source of motor neurons, conventional differentiation protocols are lengthy, variable, and unsuitable for high-throughput applications. To overcome these challenges, bit.bio developed opti-ox™, a deterministic cell programming technology that enables rapid and reproducible generation of specific cell types. Using this platform, we created ioMotor Neurons - a homogeneous

population of iPSC-derived motor neurons displaying classical morphology and robust neurite outgrowth. From day 4 onwards, these cells express key neuronal (MAP2, TUBB3), cholinergic (ChAT, VACHT), and motor neuron-specific (MNX1, ISL1/2) markers, confirmed via ICC and RT-qPCR. Single cell and bulk RNA-sequencing together demonstrate a rapid acquisition of a motor neuron identity and the generation of a highly pure cell population that can be manufactured in a consistent manner. In addition, MEA analysis showed that the neurons are functional as they demonstrate an increasing spontaneous neuronal activity over 40 days and as expected did not form synchronous neuronal networks. To enhance screening specificity and accelerate ALS drug discovery, we used CRISPR/Cas9 to generate a panel of ioDisease Model motor neurons carrying disease-relevant mutations in SOD1, FUS, and TARDBP (TDP-43). To further enable high-throughput functional genomics, we developed CRISPRko-Ready ioMotor Neurons, which constitutively express Cas9. This platform supports efficient genome-wide screening and reduces gene-editing timelines from months to days. Proof-of-concept studies confirmed effective single-gene knockout of SOX11 via lentiviral gRNA delivery. Together, our opti-ox technology provides a scalable and reproducible platform for generating iPSC-derived motor neurons, enabling applications in disease modelling, drug screening, and functional genomics for ALS and related disorders.

Disclosures: **T. Oosterveen:** A. Employment/Salary (full or part-time): bit.bio. **L. Foulser:** A. Employment/Salary (full or part-time): bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time): bit.bio. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time): bit.bio. **T. Brown:** A. Employment/Salary (full or part-time): bit.bio. **S. Milde:** A. Employment/Salary (full or part-time): bit.bio. **K. Firth:** A. Employment/Salary (full or part-time): bit.bio. **O. Dovey:** A. Employment/Salary (full or part-time): bit.bio. **B. Newman:** A. Employment/Salary (full or part-time): bit.bio. **H. Garnett:** None. **V. Yianni:** A. Employment/Salary (full or part-time): bit.bio. **S. Salic-Hainzl:** A. Employment/Salary (full or part-time): bit.bio discovery. **S. Barbaria:** A. Employment/Salary (full or part-time): bit.bio discovery.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.04/Web Only

Topic: F.09. Motor Neurons and Muscle

Title: Computational analysis of conserved RNA-binding proteins influencing neuromuscular junctions in aging

Authors: *S. JHA¹, N. M J²;

¹SASTRA Deemed Univ., Thanjavur, India; ²Biotech., SASTRA Deemed Univ., Bengaluru, India

Abstract: Sarcopenia (weakening of muscles with age) is a prevalent neuromuscular condition contributing to age-associated disabilities. As muscle function relies on the neural control brought about by neuromuscular junctions (NMJs), it would be important to examine the functioning of NMJs which in turn controls muscle activity (Rodríguez Cruz et al. 2020; Front. Mol. Neurosci. 13, Verdile et al. 2021; Cells 10:1-19). NMJs are highly disease-prone, complex synapses central to the neural control of muscle activity. In this context, it would be important to identify molecular regulators underlying altered NMJ biology during aging, contributing to muscle weakening. The present work aims to explore conserved RNA-binding proteins (RBPs) in major model organisms (*C. elegans*, *D. melanogaster*, *D. rerio*, and *M. musculus*), and humans, potentially controlling gene expression patterns in NMJs/muscle tissues. Herein, we identified the conserved RBPs potentially regulating NMJ functioning in the selected species, followed by the analysis of their expression levels during aging. A number of RBP families including helicases and Cytoplasmic Polyadenylation Element Binding (CPEB) proteins showed remarkable expression patterns in aged samples in comparison with young muscles. Further studies in this regard would facilitate better understanding of the molecular regulatory processes controlling aging and also identify potential novel targets for therapy.

Disclosures: S. Jha: None. N. M j: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.05/P4

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant R01-NS026539

Title: Location-independent axon pathfinding by cranial relay neurons in the hindbrain of larval zebrafish

Authors: A. TRACY, *K. L. MCARTHUR;
Southwestern Univ., Georgetown, TX

Abstract: During early brain development, motor neurons in the hindbrain must receive appropriate synaptic inputs to drive behavior. The role of motor neuron positioning in that process is still unclear. For example, facial branchiomotor neurons (FBMNs) in larval zebrafish generate feeding and breathing behaviors and normally migrate from rhombomere 4 (R4) to rhombomere 6 (R6) by 2 days post-fertilization (dpf). However, migration mutants (in which FBMNs fail to migrate out of R4) can still produce functional feeding and breathing behaviors. This suggests that premotor neurons can extend their axons to form synapses on FBMNs, even when FBMNs are in the “wrong” location. We investigated whether one source of synaptic input to the FBMNs, the cranial relay neurons (CRNs), remodel their axons in migration mutants to

target FBMNs. CRNs relay excitatory signals from the Mauthner cell escape circuit to cranial and pectoral motor neurons, including FBMNs. We used single-cell electroporation of fluorescent dye to trace and analyze CRN axon projections into R4 and R6 of 5dpf wild-type and *llk(rwl6)* migration mutant larval zebrafish (*D. rerio*). Tracing was completed while blinded to subject genotypes. Measures of axon branching complexity (total path length, # terminal tips, highest path order) in each rhombomere were compared between wild-type (n=6) and migration mutant (n=7) subjects, using Welch's independent t-tests. Complexity of axon branching in R6 was greater in wild-type subjects than in migration mutant subjects (total path length: p=0.0114; # terminal tips: p=0.0165; highest path order: p=0.0312). Complexity of axon branching in R4 was greater in migration mutants than in wild-types (total path length: p=0.0023; # terminal tips: p=0.00216). Thus, axon branching complexity followed FBMN location (R4 in migration mutants, R6 in wild-types). These results could not be attributed to general differences in axon complexity between wild-type and mutant subjects, as there were no significant differences in CRN axon complexity in rhombomere 2 (R2) - a region that does not contain FBMNs, in either genotype. These results are consistent with CRNs remodeling their axons to ramify in the location of FBMNs, even when FBMNs fail to migrate normally. These results may explain how FBMN circuits in migration mutants produce functional behaviors despite FBMN mispositioning. Future work will confirm that functional synapses between FBMNs and premotor neurons are actually occurring where there is increased axonal complexity, and investigate the mechanisms of this location-independent axon pathfinding in the vertebrate hindbrain.

Disclosures: A. Tracy: None. K.L. McArthur: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.06/P5

Topic: F.09. Motor Neurons and Muscle

Support: Texas A&M University

Title: Facilitation of human corticospinal excitability by personalized spinal cord ultrasound stimulation

Authors: *L. HOU, Y. LEI;
Texas A&M Univ., College Station, TX

Abstract: Low-intensity focused ultrasound has been proven to be a promising non-invasive stimulation technology with the ability to modulate spinal neural activity. This study aimed to achieve subject-specific spinal cord ultrasound stimulation (SCUS) for increasing the human corticospinal excitability. A 500 kHz four-element annular array ultrasound transducer with the

personalized focal depth was adopted to target the C8 spinal cord level for each subject. The SCUS paradigm was a 500-ms pulse train with pulse repetition frequency of 1000 Hz and duty cycle of 30% delivered every 1.5 s for a total of 10 minutes. The free-field spatial-peak pulse-average intensity (I_{SPPA}) was set as 10 W/cm². Transcranial magnetic stimulation (TMS)-elicited motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle were utilized to measure changes in corticospinal excitability before and up to 20 minutes after SCUS. Our results showed that the SCUS produced sustained increase in the amplitudes of MEPs in the FDI muscle for at least 20 minutes, whereas the sham SCUS induced no significant change. These findings suggest that the SCUS could be an effective paradigm to facilitate corticospinal drive to the muscle. It has the clinical application potential for neurological disorders treatments.

Disclosures: L. Hou: None. Y. Lei: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.07/P6

Topic: F.09. Motor Neurons and Muscle

Support: Research Grant; Granted by the University of Oklahoma - Graduate Student Senate

Title: Transcutaneous spinal direct current stimulation and motor function

Authors: *A. GIGLIOTTI, E. SURUCU, K. PENDLETON, H. PEREIRA;
Hlth. and Exercise Sci., The Univ. of Oklahoma, Norman, OK

Abstract: Transcutaneous Spinal Direct Current Stimulation (TSDCS) has the potential to modulate the α -motor neurons and induce functional changes. However, the efficacy of TSDCS in modulating the excitability of the corticospinal tract and motor performance in humans is equivocal. The purpose of this study was to determine if anodal and cathodal TSDCS can alter motor performance and corticospinal excitability of the dorsiflexor muscles compared to a sham stimulation. 13 healthy individuals (26.3 ± 8.8 years old; 7 Men and 6 Women) received 3 different conditions of TSDCS (anodal, cathodal, and sham) on separate test sessions. TSDCS was delivered at 2.5 mA for 15 minutes (charge density: 0.018 mAh/cm²) with an active electrode on T10 and two reference electrodes on the iliac crests. Transcranial magnetic stimulation (TMS)-evoked twitches were used to assess the voluntary activation (VA) of the dorsiflexor muscles. At 10% of maximal voluntary contraction (MVC), TMS-induced motor evoked potentials (MEPs) were recorded at the active motor threshold (AMT) and at 120% of AMT, along with the stimulator intensity required to elicit AMT. Women and men showed distinct modulation of AMT immediately after anodal and cathodal TSDCS (Women: 35.3 ± 4.8 , 38.3 ± 6.4 , 35 ± 4.1 ; Men: 39.1 ± 7.2 , 37.4 ± 6.3 , 37.7 ± 5.1 , respectively for anodal, cathodal,

and sham, Condition $\times$ Sex: $p = 0.008$). The MEP amplitude at AMT and 120% AMT was not modulated by TSDCS ($p > 0.05$). TSDCS did not change VA or RFD at any time point (all $p > 0.05$). This preliminary data suggests that cathodal TSDCS may modulate the excitability of the corticospinal tract in a sex-dependent manner. However, these alterations were not reflected by changes in RFD of the dorsiflexor muscles, and other tasks should be investigated.

Disclosures: A. Gigliotti: None. E. Surucu: None. K. Pendleton: None. H. Pereira: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.08/P7

Topic: F.09. Motor Neurons and Muscle

Title: Therapeutic Targeting of Mitochondrial Imbalance and Lipid Accumulation in SPG11-HSP

Authors: *S. PERIYAPALAYAM MURALI¹, G. THAKUR², Z. CHEN³, X.-J. LI⁴;
¹Univ. of Illinois Col. of Med., Rockford, IL; ²Univ. of Illinois, Chicago, Rockford, IL; ³Univ. of Illinois at Chicago, Rockford, IL; ⁴Dept. of Biomed. Sci., Univ. of Illinois, Rockford, IL

Abstract: Background: Hereditary spastic paraplegias (HSPs) are genetic disorders causing progressive lower limb weakness and spasticity. SPG11, the most common autosomal recessive form, disrupts spatacsin function, leading to pathological changes, including mitochondrial and lipid metabolism defects. This project aims to regulate the MFN2 to improve mitochondrial dynamics and investigate the impact of LXR agonists on lipid dysfunction and its link with the mitochondrial pathway. With no cure available, targeting these pathways offers a promising strategy to slow disease progression. **Hypothesis:** In SPG11-HSP, excessive mitochondrial fission and reduced fusion (due to low MFN2) disrupt cellular homeostasis. This study will test the hypothesis that enhancing MFN2 will improve mitochondrial dynamics. Clearing lysosomal cholesterol with LXR agonists may further stabilize mitochondria and enhance MFN2-lipid droplet interactions. **Study Design:** Patient-specific iPSCs are generated and differentiated into cortical projection neurons to study disease-related pathological changes. A lentiviral vector expressing MFN2 enables efficient neuronal expression to enhance mitochondrial function. Additionally, impaired lipid metabolism will be targeted by using LXR agonists to clear lysosomal cholesterol accumulation and evaluate its effect on the MFN2-lipid metabolic pathway. **Results:** Gene and protein expression analysis confirmed successful iPSC generation and differentiation into cortical projection neurons. SPG11 neurons exhibited disease-specific axonal swellings, while qPCR validated proper gene expression across cell stages. Lentiviral overexpression of MFN2 successfully restored mitochondrial fusion, reduced cytotoxicity, and increased ATP levels. LXR agonist treatment cleared lysosomal cholesterol, reduced axonal swellings, and lowered caspase-3/7 activity. Importantly, LXR treatment also increased MFN2 expression and decreased TOMM20 levels, suggesting a functional link between lipid

metabolism and mitochondrial dynamics. **Conclusion:** These findings support the hypothesis that targeting both pathways can synergistically improve neuronal health in SPG11-HSP.

Disclosures: S. Periyapalayam Murali: None. G. Thakur: None. Z. Chen: None. X. Li: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.09/P8

Topic: F.09. Motor Neurons and Muscle

Title: Mapping spinal neuron firing patterns to behavioral outputs using maximal noise entropy

Authors: *W. QIN^{1,2}, P. MEKDARA⁴, A. LEVINE⁵, T. O. SHARPEE³;

¹UC San Diego, San Diego, CA; ²Cnl-t, Salk Inst., La Jolla, CA; ³CNL-T, Salk Inst., San Diego, CA; ⁴Spinal Circuits and Plasticity Unit, Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; ⁵NIH, Bethesda, MD

Abstract: Understanding the functional connectivity of spinal neurons is essential for elucidating the mechanisms underlying motor control. Neurons in the spinal cord are organized into distinct laminae, each receiving varied sensory and interneuronal inputs and projecting to specific muscle groups. This laminar organization suggests potential functional specializations for mediating different types of motor outputs, such as rapid reflexive movements versus sustained voluntary actions. In this study, we applied the Maximum Noise Entropy (MNE) framework to map spinal neuron firing patterns to motor outputs in awake, behaving mice. MNE provides advantages over traditional spike-triggered methods, such as spike-triggered average (STA) or spike-triggered covariance (STC), particularly when dealing with naturalistic, non-Gaussian stimuli. By minimizing assumptions about stimulus distributions, MNE facilitates a more unbiased estimation of neural receptive fields. We obtained neural spike train data from high-density electrophysiological recordings of single-unit activity in the spinal cords of vertebral-fixed, optogenetically stimulated mice. Concurrent behavioral recordings were performed to track limb movements during self-driven locomotion. Preliminary analyses using linear MNE filters indicated distinct excitatory and inhibitory correlations between individual neuron firing patterns and motor outputs, suggesting some neurons may have stronger associations with specific motor behaviors. Additionally, we used the spike time tiling coefficient (STTC) to quantify temporal correlations between spike trains across different laminae, aiming to explore inter-laminar functional connectivity.

Disclosures: W. Qin: None. P. Mekdara: None. A. Levine: None. T.O. Sharpee: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.10/P9

Topic: F.09. Motor Neurons and Muscle

Title: Scyl1 functions outside of previously identified pathways to maintain post-natal development and motor function

Authors: A. KOIRALA, S. BARE, M. TOUBIN, K. O'CONNOR, A. VYDRA, D. THOMAS, H. CHEN, *S. PELLETIER;
Indiana Univ., Indianapolis, IN

Abstract: SCYL1 deficiency syndrome is a rare pediatric disorder characterized by early-onset liver dysfunction and progressive neurodegeneration, leading to motor and cognitive decline. Although pathogenic mutations in *SCYL1* are well documented, the molecular mechanism underlying disease pathogenesis remains unclear, largely due to an incomplete understanding of SCYL1 protein function. Here we report that SCYL1 exerts its essential biological roles independently of its canonical molecular partners. Using an allelic series of 13 *Scyl1* separation-of-function mutations engineered by modifying the endogenous *Scyl1* locus in mice, we systematically disrupted specific or groups of interactions and assessed their contribution to disease phenotypes. Remarkably, disruption of SCYL1 interactions with previously implicated partners - including components of the COPI coatomer complex, GORAB, and others - did not result in overt phenotypes. By contrast, mutations affecting SCYL1 oligomerization and membrane association led to hallmark features of SCYL1 deficiency as do *Scyl1*-knockout animals. These findings suggest that SCYL1 acts primarily through membrane-associated structural or scaffolding mechanisms, redefining its role in cellular physiology and disease.

Disclosures: A. Koirala: None. S. Bare: None. M. Toubin: None. K. O'Connor: None. A. Vydra: None. D. Thomas: None. H. Chen: None. S. Pelletier: None.

Poster

PSTR029: Motor Neurons: Development, Identification, Intrinsic Properties, and Modulation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR029.11/P10

Topic: F.09. Motor Neurons and Muscle

Support: UQ Postgraduate Scholarship (CL)
UQ Postgraduate Scholarship (PT)

Australian NHMRC grant 569827 (MB)
Australian NHMRC grant APP1065884 (MB)

Title: Alfaxalone decreases glycinergic neurotransmission to rat brainstem motor neurons by cannabinoid 1 receptor activation

Authors: C. LAU¹, P. P. THAKRE¹, *M. C. BELLINGHAM²;

²Sch. of Biomed. Sci., ¹Univ. of Queensland, Brisbane, Australia

Abstract: Alfaxalone at anesthetic doses inhibits glycinergic transmission to rat hypoglossal motoneurons (HMNs). This reduction in inhibitory activity is consistent with motor excitation during alfaxalone anesthesia. We investigated the effects of alfaxalone on HMNs in the presence of the cannabinoid 1 receptor (CB₁R) agonist WIN55,212-2, the CB₁R inverse agonist AM251, and the CB₁R antagonist NESS0327, using whole cell patch clamp techniques under voltage clamp conditions. Whole-cell recordings were performed on HMNs in brainstem slices from 10-14 day-old Wistar rats. Spontaneous and evoked inhibitory post-synaptic currents (IPSCs) were recorded at a holding potential of -60mV, using a CsCl-based internal solution, in the presence of the non-NMDA and NMDA glutamate receptor blockers NBQX (10μM), APV (50μM) and the GABA_AR antagonist bicuculline (5μM). A WIN55,212-2 dose-response study was performed with bath application of 10nM, 30nM, 100nM, 300nM, 1μM and 3μM WIN55,212-2. WIN55,212-2 significantly decreased evoked IPSC amplitude to $50.85 \pm 17.20\%$ of control at 10nM showing a dose-dependent decrease to $41.41 \pm 18.85\%$ of control at 3μM concentration. Non-linear fitting of a dose-response curve yielded an EC₅₀ value of 18 nM. Subsequent studies involved pre-application of WIN55,212-2 (300nM), AM251 (1μM), NESS0327 (100pM), or the non-specific TRP channel blocker 2-APB (100μM), followed by application of 1μM, 3μM or 10μM of alfaxalone. Significant spontaneous IPSC amplitude depression was apparent from 3μM alfaxalone and reduced IPSC frequency was apparent from 10μM alfaxalone in the presence of WIN55,212-2. AM251 (1μM) and NESS0327 (100pM) blocked evoked IPSC amplitude reductions and evoked IPSC event prolongation by alfaxalone. No significant changes in spontaneous IPSC peak amplitude, frequency, half-width, decay time, or baseline holding current were apparent on co-application of 2-APB and alfaxalone. Our data suggest that alfaxalone causes a reduction in glycinergic transmission via the endocannabinoid signaling pathway and produces an inward current through the activation of TRP channels. The suppression of glycinergic inhibition is consistent with motor excitation, analogous to that seen in strychnine poisoning. An anesthesia combination comprising alfaxalone with a CB₁R antagonist, could potentially motor excitation and markedly improve alfaxalone anesthesia in laboratory rodents and other species.

Disclosures: C. Lau: None. P.P. Thakre: None. M.C. Bellingham: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Jurox Pty Ltd.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.01/P11

Topic: G.02. Neuroendocrine Processes and Behavior

Support: SNSF

Title: From metabolism to memory: exploring amylin's role in the hippocampus

Authors: *G. MAZZINI¹, I. GEZGINER³, C. LE FOLL⁴, T. A. LUTZ²;

¹Inst. of Vet. Physiol., ²Univ. of Zurich, Zurich, Switzerland; ³Inst. for Biomed. Engineering, Dept. of Information Technol. and Electrical Engineering, ETH Zurich, Switzerland, Zürich, Switzerland; ⁴Inst. of Vet. Physiology, Univ. of, Zuerich, Switzerland

Abstract: Amylin, a hormone co-secreted with insulin by pancreatic β -cells in response to nutrient intake, acts as a satiation signal. Amylinomimetics are approved treatments for diabetes and obesity management thanks to their regulatory effects on appetite and glucose metabolism. Although amylin's effects on eating behavior are well-documented, its broader physiological functions still need to be uncovered. Here, we investigated amylin's novel role in hippocampal function and memory processing. Using resting-state fMRI, we examined how amylin (500 μ g/kg) and a long-acting amylin receptor agonist salmon calcitonin (sCT; 10 μ g/kg) affect hippocampal connectivity in wild-type (WT) mice compared to knock-out (KO) mice lacking amylin receptor fundamental components. Both compounds induced significant changes in hippocampal connectivity patterns in WT mice but not in KO mice, highlighting the critical role of intact amylin receptor signaling in mediating these responses. c-Fos expression in the hippocampus was higher in amylin-injected and sCT-injected mice than in vehicle-injected mice, suggesting increased neuronal activity in this area. Through novel object recognition and novel location recognition behavioral studies, we showed that amylin-treated WT mice significantly improved object recognition and spatial memory, while sCT treatment did not enhance memory performance. Interestingly, in a rat model, both amylin- and sCT-injected rats demonstrated an improved ability to recognize objects and spatial locations compared to vehicle-injected rats. These findings establish amylin as a significant modulator of hippocampal function and memory processing, representing a previously unrecognized role for this metabolic hormone in cognitive function. Our results not only advance the understanding of amylin's physiological functions but also suggest a promising therapeutic venue for cognitive disorders, including dementia and Alzheimer's disease, where effective treatment options are unfortunately still limited.

Disclosures: G. Mazzini: None. I. Gezginer: None. C. Le Foll: None. T.A. Lutz: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.02/P12

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NSF IOS-2050260
NSF IOS-2050230

Title: Transcript Level Analysis of the Effect of Estradiol Provision in the Hippocampus on Distal Brain Structures

Authors: *C. HARVEY¹, A. ST JEAN², E. PRYOR², D. J. BAILEY⁴, C. J. SALDANHA³;
¹American Univ., Alexandria, VA; ³Neurosci., ²American Univ., Washington, DC; ⁴Biol., St. Norbert Col., De Pere, WI

Abstract: The developing and adult zebra finch brain has every enzyme necessary to synthesize estradiol (E2) from cholesterol. The hippocampus (HP) is a site of abundant E2 synthesis, and inhibition of E2 synthesis impairs spatial memory performance. The HP, diencephalon, and caudomedial nidopallium (NCM), are all aromatase rich areas. Whereas the HP projects directly to the diencephalon in songbirds, there are no known direct connections with the NCM. We wondered if local manipulation of estradiol synthesis in the HP may modulate steroidogenic enzyme or steroid receptor expression in distal regions of the brain. We also examined if this potential modulatory effect is dependent on connections of the HP with these distal brain areas. Birds were given a silastic implant (SIL) above the HP (control) or one containing the GABA-A receptor (GABA-AR) enhancer allopregnanolone. Within those groups, birds were also treated with either (SIL), the aromatase-inhibitor ATD, or ATD with estradiol (E2) replacement (ATDE2). We measured the expression of the steroidogenic enzymes 3betaHSD, 5alpha reductase, aromatase, and the steroid receptors for androgen (AR), estrogen receptors alpha and beta (ERalpha; ERbeta), and the membrane receptor GPER in the diencephalon and the NCM. GABA-AR enhancement in the HP increased the expression of 3betaHSD, but not 5-alpha-reductase or aromatase in the diencephalon. Further, estrogen receptor alpha (ERalpha) expression, but not androgen receptor, ERbeta, or GPER, increased in the diencephalon. There was no effect of GABA-AR enhancement on any gene targets in the NCM. In addition, there were no effects of aromatase inhibition or E2 replacement on any of the gene targets in either the diencephalon or the NCM. The data suggest that local enhancement of HP inhibition may affect steroidogenic enzyme and estrogen receptor expression at efferent targets, but not at unconnected brain regions. This indicates that inhibitory projections from the HP may modulate the steroidal milieu and steroid action at distal sites of the vertebrate brain.

Disclosures: C. Harvey: None. A. St Jean: None. E. Pryor: None. D.J. Bailey: None. C.J. Saldanha: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.03/Q1

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NSF IOS-2050260
IOS-2050230

Title: The effects of aromatase inhibition and estradiol replacement on the hippocampal transcriptome of the zebra finch

Authors: R. ANDRADE¹, Y. NAU², E. BASHAW³, D. J. BAILEY⁵, J. BRACHT⁴, *C. J. SALDANHA⁴;

¹American Univ., New Milford, CT; ²American Univ., Sharon, MA; ³American Univ., Renton, WA; ⁴American Univ., Washington, DC; ⁵Biol., St. Norbert Col., De Pere, WI

Abstract: Estrogens like estradiol (E2) are synthesized from testosterone (T) by the enzyme aromatase. In the songbird brain, the hippocampus (HP), a telencephalic structure critical for learning and memory, is a major site of E2 synthesis where aromatase is readily detectable in both sexes and is particularly abundant at synaptic loci. Decreases in local E2 synthesis via the aromatase inhibition in the zebra finch HP, impairs spatial memory performance to the same extent as HP-lesioned birds. Aromatase inhibition with concomitant replacement with either E2, or with an agonist of the membrane E2 receptor GPER however, restores memory function back to control levels. These data suggest that local, perhaps synaptic aromatization, may be a crucial modulator of memory function in songbirds, an effect that is dependent upon GPER. The genomic mechanisms and gene clusters underlying these observations, however, are unknown. This project seeks to understand the transcriptional changes that may contribute to the poor spatial memory performance in zebra finches with low local E2 synthesis in the HP. mRNA from three treatment groups (control, ATD, and ATD with E2 replacement) was sequenced (Illumina) and a traditional RNAseq analysis (HISAT, Stringtie, and DESeq2) pipeline was performed. Weighted gene correlation network analysis (WGCNA) sorted 18,295 genes into 44 modules identifying correlations of sex and treatment, hub genes, and most notably, created two distinct modules of genes for either sex, showing a distinct dimorphism. Gene ontology analysis was performed to understand biological processes and molecular pathways involved in changes of the local HP endocrine environment upon inhibition of HP aromatase and provision of E2. Significant terms revealed positive regulation of ERK1, ERK2, MAPK, and phospholipase C cascades, as well as positive enrichment of synaptic, neurogenic, and axonogenic processes related to memory. Current work uses RT-qPCR to validate prior observations by examining expression of identified hub genes, like GPER and NMSF, in HP of adult finches treated orally with PBS or the aromatase inhibitor, fadrozole.

Disclosures: R. Andrade: None. Y. Nau: None. E. Bashaw: None. D.J. Bailey: None. J. Bracht: None. C.J. Saldanha: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.04/Q2

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH R01AG041374

Title: Effect of novel environment on fiber photometry cholinergic release dynamics in the hippocampus of female wild-type and ER α -knockout mice

Authors: *J. C. FLANNERY¹, J. M. DANIEL²;

²Psychology, Neuroscience, Brain Inst., ¹Tulane Univ., New Orleans, LA

Abstract: Cognitive processes mediated by the hippocampus are sensitive to effects of estradiol (E2). E2 enhances hippocampal function, partially through facilitating basal forebrain cholinergic signaling to the hippocampus. A substantial subset of basal forebrain cholinergic neurons express estrogen receptors (ERs), but the specific contributions of different ERs to novelty-induced basal forebrain cholinergic release in the hippocampus remain unclear. The goal of the present study is to determine whether ER α -knockout (KO) mice demonstrate reduced novelty-induced cholinergic release in the hippocampus relative to their wild-type (WT) counterparts. We used the targeted viral transfection of an acetylcholine (ACh) G-protein coupled receptor activation-based (GRAB_{ACh3.0}) sensor and fiber photometry recording to address this question. To control for the supraphysiological E2 levels seen in ER α KO mice, both WT and ER α KO mice were ovariectomized (OVX) and implanted with subcutaneous E2 capsules that maintain physiological circulating E2 levels. All mice received a viral injection of GRAB_{ACh3.0} and a fiberoptic cannula implant targeted to CA1 of the right hippocampus. Testing was conducted ~7 weeks later. Mice were habituated for 5 minutes per day for 3 days to one side (familiar) of a two-chamber apparatus. On the fourth day, GRAB_{ACh3.0} fluorescent signals were recorded using Synapse software. Mice were placed in the familiar side for 5 minutes before the door to the other side (novel) was opened, where the mice spent an additional 5 minutes. The novel side contained two objects and wall cues. Recording data were analyzed for 30 seconds pre as compared to 30 seconds post door opening. Results revealed a significant rise in endogenous ACh release in CA1 of the hippocampus post door opening, as indicated by average area-under-the-curve values from normalized $\Delta F/F$ traces of GRAB_{ACh3.0} fluorescent signals. However, preliminary results show this increase does not vary significantly by genotype. Results indicate that exposing mice to a novel environment induces a rapid increase in cholinergic release in the hippocampus and suggest that ER α is not involved in modulating this effect. Work is ongoing to determine the mechanisms by which E2 may be influencing this release.

Disclosures: J.C. Flannery: None. J.M. Daniel: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.05/Q3

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant P01AG071746

Title: Effects of different estradiol treatment regimens on myelin-associated protein levels in the frontal cortex and hippocampus of aging ovariectomized rats

Authors: C. MONTANARI, B. P. PETHE, K. R. SALEM, *J. M. DANIEL;
Tulane Univ., New Orleans, LA

Abstract: Age-related cognitive decline is linked to white matter shrinkage. In women, some but not all reports support a role for menopausal estrogen therapy in maintenance of white matter integrity during aging. The goal of the current work was to determine how the timing of estradiol administration impacts its ability to affect protein markers of white matter in the frontal cortex and hippocampus in a rat model of menopause. Female Long-Evans rats were ovariectomized at 12 months of age and received Silastic capsule implants containing vehicle or estradiol. Capsules were replaced after 40 days and again after 5 months resulting in the following treatment groups: 1) Continuous Vehicle (received only vehicle capsules; modeling women who never use menopausal estrogen therapy), 2) Continuous Estradiol (received only estradiol capsules; modeling women who take and remain on estrogen therapy), 3) Previous Estradiol (received estradiol for 40 days followed by vehicle; modeling women who take estrogen for few years and then stop), and 4) Delayed Estradiol (received vehicle for 6 months followed by 4 months of estradiol; modeling women who begin taking estrogen years after menopause). Rats were euthanized at 22 months of age. Two myelin-associated proteins, myelin basic protein (MBP) and myelin proteolipid protein (PLP), were measured in the frontal cortex and hippocampus by western blotting. The Continuous Estradiol group had significantly increased levels of MBP and PLP in the frontal cortex as compared to all other groups. The Previous Estradiol and Delayed Estradiol groups did not differ from Continuous Vehicle. No significant group differences were observed in the hippocampus. Results indicate that both the timing of the initiation and the duration since its termination impact the ability of estradiol treatment to support white matter integrity in the frontal cortex of aging female rats.

Disclosures: C. Montanari: None. B.P. Pethe: None. K.R. Salem: None. J.M. Daniel: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.06/Q4

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant R01AG041374

Title: Molecular phenotype of hippocampus in female mice lacking membrane estrogen receptor alpha

Authors: *P. S. TIRRELL¹, K. R. SALEM², B. A. MENON³, J. M. DANIEL⁴;
¹Neurosci. Program, ²Psychology, Tulane Univ., New Orleans, LA; ³Tulane Univ., Neuroscience Program, LA; ⁴Psychology, Neuroscience, Brain Inst., Tulane Univ., New Orleans, LA

Abstract: Estrogens play a critical role in supporting cognitive function through their actions in the hippocampus, a brain region essential for learning and memory. In addition to classic genomic signaling, estrogens exert rapid effects via membrane-bound estrogen receptors (mERs), including membrane-localized estrogen receptor alpha (mER α). Prior research suggests that activation of mER α facilitates memory formation and synaptic plasticity, but the downstream molecular pathways supporting these effects are not fully known. Here, we use a genetically modified mouse model, the nuclear-only estrogen receptor alpha (NOER) mouse, in which a C451A point mutation precludes ER α membrane localization, thereby eliminating membrane-initiated signaling while preserving nuclear function. We previously demonstrated that female NOER mice make significantly more retroactive errors on the 8-arm radial maze task, a hippocampal-dependent spatial memory task, suggesting impaired delay-dependent memory. To investigate the molecular mechanisms underlying these deficits, we first examined expression of key intracellular signaling proteins in hippocampal lysates from young adult wild-type (WT, n = 5) and NOER (n = 7) mice via western blot analysis. Compared to WT, NOER exhibited elevated total ERK2, decreased total Akt, and decreased total CREB protein levels despite no significant differences in phosphorylation states, suggesting altered pathway regulation rather than acute signaling deficits. Next, we performed bulk RNA sequencing on hippocampal lysates from female WT (n = 6) and NOER (n = 6) mice. Differential expression analysis identified several transcripts that were significantly altered in NOER hippocampus, including significant downregulation of *Cacng5*, which encodes the type II TARP gamma5, a key regulator of AMPA receptor trafficking and gating. To more comprehensively assess the molecular phenotype of NOER hippocampus, we are currently performing proteomic quantitative analysis of hippocampal lysates from female WT and NOER mice (12-14 weeks old, n = 5 per group). Mass spectrometry-based profiling will identify differentially expressed proteins and enriched signaling pathways that may be disrupted by the loss of mER α . Given the robust memory deficit observed in NOER mice, we anticipate changes in proteins related to synaptic plasticity, intracellular signaling cascades, and neurotrophic pathways involved in memory. Together, these studies will elucidate the molecular landscape shaped by membrane-initiated estrogen signaling and identify specific targets through which membrane-initiated estrogen signaling supports cognitive function.

Disclosures: P.S. Tirrell: None. K.R. Salem: None. B.A. Menon: None. J.M. Daniel: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.07/Web Only

Topic: G.02. Neuroendocrine Processes and Behavior

Title: Hippocampus-synthesized estrogen and androgen modulate dendritic spines and LTP in non-genomic manner

Authors: *S. KAWATO;
Univ. of Tokyo, Tokyo, Japan

Abstract: We have demonstrated (1) hippocampal synthesis of estrogen and androgen, and (2) non-genomic synaptic modulation by these sex-steroids. [Synthesis] We showed expression as well as neuronal/synaptic localization of essential enzymes in the adult male rat hippocampus. Mass-spectrometric analysis demonstrated that hippocampal levels of estradiol (E2), testosterone (T) and dihydrotestosterone (DHT) are about 8 nM, 17 nM and 7 nM, higher than those in plasma. Rapid E2 synthesis within the hippocampus can be measured via blocking of LTP (long-term potentiation) by 20 min perfusion of Aromatase inhibitor in hippocampal slices. Castration did not decrease male hippocampal E2, because E2 is synthesized from hippocampal T. Castration, however, significantly decreased T and DHT in the hippocampus, indicating a transport of T via the blood circulation. Female hippocampal levels of E2 (0.5-4 nM), and T (1 nM) are less than male, but much higher than those in plasma. [Synaptic Modulation] E2-induced rapid non-genomic modulation (1 h) was demonstrated by analysis of dendritic spines and LTP of adult rat hippocampal 'acute' slices (steroid-depleted slices). Dendritic spine analysis was performed for CA1 pyramidal neurons in hippocampal slices. Spine density and spine head diameters were obtained by mathematical software Spiso-3D which identifies spines by calculating geometrical parameters. E2 at 1 nM rapidly increased the density of small-head spines. T and DHT at 10 nM increased the density of small-head and large-head spines. Signaling pathways are: synaptic ER α or AR $\rightarrow$ LIMK, MAPK, PKA, PKC, Src $\rightarrow$ cofilin or cortactin $\rightarrow$ actin polymerization $\rightarrow$ new spine formation. LTP analysis showed that 1 nM E2 induced full-LTP (E2-LTP) upon sub-threshold stimulation, although without E2 the sub-threshold stimulation did not induce full-LTP. Kinase inhibitors against MAPK, PKA, PKC, LIMK, Src blocked E2-LTP. References: Kimoto et al., 2001 Endocrinol, Hojo et al., 2004 PNAS, Mukai et al., 2007 J. Neurochem, Hojo et al., 2009 Endocrinol, Mukai et al. 2011 Cereb Cortex, Ooishi et al. 2011 Cereb Cortex, Okamoto et al., 2012, PNAS, Kato et al., 2013, Frontier Neurosci. Hasegawa et al., 2015 Brain Res., Hatanaka et al., 2015 Brain Res., Murakami et al., 2015 Brain Res., Soma et al., 2018 Frontier Neurosci., Hojo and Kawato 2018 Frontier Neurosci., Kawato et al. 2025 medRxiv.

Disclosures: S. Kawato: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.08/Q5

Topic: G.02. Neuroendocrine Processes and Behavior

Support: JSPS KAKENHI Grant-in-Aid for Scientific Research(B)
JSPS KAKENHI Grant-in-Aid for Challenging Research (Exploratory)

Title: Neurosteroids involved in spatial memory and analysis of their molecular response in the mouse brain

Authors: *K. SHIMIZU¹, Y. ASANO², K. MAEHATA³, Y. FUKADA³;
¹Univ. of Toyama, Toyama, Japan; ²Nihon Univ., Chiba, Japan; ³Sch. of Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Neurosteroids are a group of steroid hormones synthesized from cholesterol in the brain. 7 α -hydroxy-neurosteroids (7 α -hydroxypregnenolone [7 α -OH-Preg] and 7 α -hydroxydehydroepiandrosterone [7 α -OH-DHEA]) are synthesized by a new member of the P450 hydroxylase family, CYP7B1. CYP7B1 was expressed widely in the mouse brain with high levels in the hippocampus. We identified the presence of 7 α -OH-Preg and 7 α -OH-DHEA in the mouse hippocampus after the Morris's water maze task using LC-MS/MS. *Cyp7b1* deficiency impaired remote spatial memory, whereas recent memory was mostly unaffected. Hippocampal dendritic spine densities were reduced in *Cyp7b1*-deficient mice. Spine densities were no longer increased by training in *Cyp7b1*-deficient mice, although spine densities were significantly increased by training in wild-type mice. Furthermore, chronic intracerebroventricular administration of 7 α -OH-Preg and 7 α -OH-DHEA improved the spine density and remote spatial memory performance in *Cyp7b1*-deficient mice. Notably, remote spatial memory impaired by *Cyp7b1* deficiency was more significantly rescued by administration the mixture of 7 α -hydroxylated steroids than by administration of the single neurosteroid. We concluded that the 7 α -hydroxylated neurosteroids are required for synaptic remodeling for the long-term maintenance of spatial memory in mice (iScience 2020). RNAseq results from the administration of the neurosteroids in the *Cyp7b1* KO mouse showed that a group of molecules involved in neurological disorders are altered. We are elucidating the molecular mechanism of spine remodeling and spatial memory maintenance by neurosteroids using transcriptomic analysis.

Disclosures: K. Shimizu: None. Y. Asano: None. K. Maehata: None. Y. Fukada: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.09/Q6

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant 5R01AG069970-03
CFNRE Trainee Pilot Grant

Title: Dietary Phytoestrogen Improves Learning and Memory in Estrogen-Deficient Rabbits

Authors: *E. A. IREWOLE, D. WANG, D. E. TALKINGTON, N. LAL, L. D. BAYS, M. D. SMITH, R. W. BELL, B. G. SCHREURS;
Neurosci., West Virginia Univ., Morgantown, WV

Abstract: Observational studies have reported a higher risk of Alzheimer's disease (AD) in women, particularly postmenopausal women. Attempts to mitigate this risk and rescue cognitive decline by administering exogenous estrogen have yielded conflicting results, highlighting a need to examine other compounds that can improve cognition and lower AD risk in postmenopausal conditions.

In this study, we investigated whether the phytoestrogen genistein administered via a diet could improve cognition and diminish AD risk in estrogen-deficient (menopausal) conditions. We modeled estrogen deficiency in New Zealand White rabbits via bilateral gonadectomy (GDX) or sham (sGDX) surgery. The rabbits were divided into four experimental groups: the first group received GDX with genistein (GN) diet, the second group received GDX with control (CON) diet, the third group received sGDX with GN diet, while the last group received sGDX with CON diet. The rabbits received their respective diets for eight weeks before undergoing cognitive assessment with trace eyeblink conditioning.

The results show that the genistein diet improved learning and memory in estrogen-deficient rabbits, as indicated by the significantly higher levels of conditioned responses and delayed recall. However, the genistein diet had no additive effect on the cognitive performance of the sham-operated rabbits. The results indicate that dietary genistein is neuroprotective in estrogen-deficient conditions and may be beneficial in rescuing cognitive decline and potentially mitigating AD risk in postmenopausal women.

Disclosures: E.A. Irewole: None. D. Wang: None. D.E. Talkington: None. N. Lal: None. L.D. Bays: None. M.D. Smith: None. R.W. Bell: None. B.G. Schreurs: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.10/Q7

Topic: G.02. Neuroendocrine Processes and Behavior

Support: Wisconsin Partnership Program at the University of Wisconsin School of Medicine and Public Health

Title: Early Adolescent Treatment with a Gonadotropin-Releasing Hormone Agonist Alters Matrix Metalloproteinase-9 Levels within the Ventral Hippocampus

Authors: *A. K. JOHNSON¹, A. NGUYEN², A. P. AUGER³;

¹Neurosci. Training Program, ²Integrative Biol., ³Neurosci. Training Program and Integrative Biol., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Perineuronal nets (PNNs) are condensed extracellular matrix (ECM) structures that surround cells and modify synaptic plasticity within the brain. Matrix metalloproteinases (MMPs) are proteases involved in ECM remodeling and their actions can be inhibited by tissue inhibitors of matrix metalloproteinases (TIMPs). Therefore, MMPs and TIMPs are important regulator factors in ECM remodeling and structural plasticity within the brain. As puberty is a significant period of neurodevelopment with changes in PNN structure and hormone levels, we postulated that treatment with a gonadotropin-releasing hormone agonist (GnRHa) would alter the mRNA levels of *Mmp2*, *Mmp9*, and *Timp2*. Our prior data show that GnRHa treatment altered pubertal maturation, as indicated by delayed vaginal opening in females and decreased testosterone levels in males. Therefore, 24 weight-matched male and female rats were injected with 0.6mg of the GnRH agonist, leuprolide acetate (LA) in depot suspension, or vehicle control, before the onset of puberty, on postnatal day (PND) 23. On PND44, corticolimbic structures, including the ventral hippocampus and amygdala, were extracted and processed for qPCR. *Mmp2*, *Mmp9* and *Timp2*, as well as two mRNA controls (*Rpl0* and *Rpl13*), were examined. Within the ventral hippocampus, there was a significant interaction between biological sex and treatment groups in *Mmp9* levels ($P=0.008$). Post-hoc interactions indicated that while there were no sex differences between male and female control groups, LA treatment significantly reduced *Mmp9* levels in males ($p=0.029$) and exhibited a trend for LA to increase *Mmp9* in females ($p=0.083$). This resulted in a sex difference in *Mmp9* levels between LA-treated males and LA-treated females ($p=0.005$). No differences were found in *Mmp2* and *Timp2* mRNA levels. Within the amygdala, no differences were found in the mRNA levels of *Mmp2*, *Mmp9*, or *Timp2*. As progesterin receptors (*Pgr*) are known to be highly induced by estradiol exposure, we examined if LA treatment resulted in lower *Pgr* mRNA levels. As expected, we found that LA treatment significantly lowered *Pgr* mRNA levels in males and females ($p=0.028$), consistent with lowering estradiol action within the ventral hippocampus. Our data suggests LA treatment can alter *Mmp9* levels within the ventral hippocampus. This suggests that exposure to GnRH agonists prior to puberty has the potential to modify PNNs and thereby synaptic plasticity within the adolescent hippocampus with potential consequence for behavior.

Disclosures: A.K. Johnson: None. A. Nguyen: None. A.P. Auger: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.11/Q8

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NSERC

Title: Mechanisms Underlying Estrogen's Rapid Facilitative Effects on Social Recognition in the Medial Amygdala of Female Mice

Authors: *C. LAROCHELLE-COMPTON;

Dept. of Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Successful social interactions rely upon the appropriate modulation of behavioural responses across different contexts, which in turn relies upon social recognition (SR). SR, the ability to distinguish between familiar and novel conspecifics, is well-established to be rapidly affected by estrogens through rapid, non-genomic mechanisms. In ovariectomized (OVX) female mice, administration of 17 β -estradiol (E2) into both the medial amygdala and hippocampus has been shown to rapidly facilitate short-term SR memory. While previous research has shown that, within the dorsal hippocampus, this facilitation requires the activation of the activation of the extracellular signal-regulated (ERK) pathway, the underlying cellular mechanism in the medial amygdala (MeA) has yet to be elucidated. Thus, the present study is investigating whether the SR and its rapid facilitation by E2 in the MeA of OVX female mice require the ERK pathway. A range of inhibiting doses of the ERK pathway inhibitor U0126 is first being used to determine the highest dose of the ERK activity inhibitor U0126 that does not block SR when administered bilaterally into the MeA. Next, the effects of ERK pathway inhibition on E2-facilitated social recognition will be investigated by infusing the highest doses that did not block social recognition before E2 administration, before mice are tested on a behavioural paradigm where control mice do not show short-term SR. It is predicted that, like in the dorsal hippocampus, inhibiting the ERK pathway in the MeA will both impair short-term SR memory and inhibit the facilitative effects of E2 administration, demonstrating that ERK activity in this region is necessary for E2's rapid facilitation of SR. This study will further our understanding of the non-genomic mechanisms that underlie estrogen's rapid modulation of memory and the medial amygdala's role in social learning and memory in females.

Disclosures: C. LaRochelle-Compton: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.12/Q9

Topic: G.02. Neuroendocrine Processes and Behavior

Support: CDMRPL-22-0-TX220320

Title: Reproductive and Developmental Effects of Ingested JP-5 Jet Fuel in Rats

Authors: *J. G. ROHAN¹, L. K. OLSEN^{1,2}, V. T. ETHRIDGE^{1,2}, E. L. ROBERTS^{1,2}, N. M. GARGAS¹, K. L. MUMY¹, W. R. HOWARD¹;

¹Naval Med. Res. Unit Dayton, WPAFB, OH; ²Leidos, Reston, VA

Abstract: The study objective is to evaluate the developmental effects induced by oral exposure to the Navy jet fuel, jet propulsion-5 (JP-5), on the first generation of offspring. Previous studies indicate that JP-5 can induce endocrine disruption. However, the effects of JP-5 mediated

endocrine disruption in offspring after pre- and post-natal exposure have not yet been investigated. Ten adult male and female Sprague Dawley rats were orally exposed to 5 or 50 mg of JP-5 per kg body weight or vehicle control for 9 weeks. After exposure, male and female rats were paired to initiate a 2-week breeding period. JP-5 exposure continued throughout the breeding period and for females throughout the gestation and nursing. A subset of immature pups underwent the righting reflex test, separation distress test, and humanely euthanized to assess hippocampal (HC) function via electrophysiological recordings. Another subset of pups was allowed to mature and underwent motor activity and novel object recognition tests, and humanely euthanized to assess HC function. Endocrine disrupting effects of JP-5 were assessed via enzyme-linked immunosorbent assay of blood plasma. Male parents and mature male and female offspring had reduced levels of progesterone. Female parents had reduced testosterone and increased thyroid stimulating hormone levels. Birth weight was significantly reduced in pups from JP-5-exposed parents. Immature pups showed a longer righting time in females but not male pups from the 5 mg/kg group compared to control. The number of distress vocalizations was reduced among immature female pups from the 5 mg/kg group compared to control pups. JP-5 had no detectable effects on recognition memory among the mature offspring. JP-5 exposed mature male offspring had increased motor activity ambulation, while females had decreased ambulation. Immature rats had reduced input-output function of HC neurons from JP-5 exposed male immature offspring but a trending increase in input-output function of HC neurons from JP-5 exposed female immature offspring. There was a small trending decrease in long term potentiation noted in both male and female immature offspring that was not statistically significant. Paired pulse facilitation (PPF) in Schaffer collateral-CA1 synapses from male and female rats found trending increases in PPF from male rats exposed to JP-5. Although no overt toxicity was observed in the parents or offspring resulting from the oral JP-5 exposure, we did detect slight differences in pup birth weight, progesterone levels, HC function and activity levels indicating that pre- and post-natal exposure to JP-5 has endocrine and neurological consequences.

Disclosures: J.G. Rohan: None. L.K. Olsen: None. V.T. Ethridge: None. E.L. Roberts: None. N.M. Gargas: None. K.L. Mumy: None. W.R. Howard: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.13/Q10

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIA Grant R01AG076030

Title: Perimenopause-induced dysregulation of the dopamine system: effects of hormone replacement therapy

Authors: *S. M. PEREZ¹, A. M. BOLEY¹, D. J. LODGE²;
¹Pharmacol., ²UT Hlth. San Antonio, San Antonio, TX

Abstract: Despite the well-documented changes in mental health associated with the menopause transition, the neural mechanisms underlying these psychiatric symptoms remain poorly understood. The perimenopausal period is characterized by an increased risk of psychiatric disorders, cognitive dysfunction, and affective disturbances, which can severely impair daily functioning in women. Emerging evidence suggests that altered regulation of the mesolimbic dopamine system, particularly by the ventral hippocampus (vHipp), may contribute to these symptoms. Importantly, both the dopamine system and its regulatory inputs are sensitive to fluctuations in ovarian hormones such as estrogen and progesterone. Our previous research has shown that the inputs from the vHipp to the nucleus accumbens (NAc) can modulate dopamine neuron activity in naturally cycling female rats. However, in the 4-vinylcyclohexene diepoxide (VCD) model of perimenopause, hyperactivity in the vHipp leads to aberrant dopamine system function. The most common therapeutic intervention for symptoms accompanying perimenopause is hormone replacement therapy (HRT); however, this treatment is highly debated due to associated risks, such as osteoporosis and heart disease. While HRT may effectively address vasomotor symptoms, its efficacy in treating neuropsychiatric symptoms remains unclear. Therefore, further research is necessary to elucidate the mechanisms underlying mood disorders during perimenopause and how these mechanisms are influenced by HRT. This study aims to determine the extent to which estrogen (17 β e) or estrogen plus progesterone (17 β e+PR) replacement prevents the dysregulation of dopamine system function and behavioral consequences in the VCD model. Our initial data suggests that increases in dopamine neuron population activity observed in VCD rats, may be normalized by chronic 17 β e administration, but not 17 β e+PR. Further, cognitive deficits observed in this model can be reversed by chronic administration of 17 β e or 17 β e+PR. Taken together, understanding how perimenopause disrupts specific neurocircuits and whether HRT prevents these disruptions is critical to the discovery of novel therapeutics to improve the quality of life for women during this transitional period.

Disclosures: S.M. Perez: None. A.M. Boley: None. D.J. Lodge: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.14/Q11

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIMH Grant R21MH136483

Title: X Chromosome dynamics in the adult female brain across the estrous cycle

Authors: *L. DEMARCHI¹, A. MILOSEVIC¹, D. ROCKS¹, J. ROWLEY², M. KUNDAKOVIC¹;

¹Fordham Univ., New York, NY; ²Dept. of Genetics, Cell Biol. and Anat., Univ. of Nebraska Med. Col., Omaha, NE

Abstract: Sex differences in behavior and brain disease risk are due to complex interactions of sex chromosomes and sex-biased gonadal hormone states across the lifespan. In women and other menstruating individuals, fluctuations in ovarian hormones and the presence of two X chromosomes may contribute to the increased risk for brain disorders such as depression and Alzheimer's disease. In particular, female-unique phenomena such as X chromosome inactivation and expression of X escapee genes are grossly understudied contributors to sex-specific neurobiology. To this end, we previously demonstrated that anxiety- and depression-related behaviors in female mice vary with the estrous cycle, with ovarian hormones influencing 3D genome dynamics and gene expression of the X chromosome in ventral hippocampal neurons. Here we aim to reveal whether these changes affect the active or inactive X chromosome, or both. We hypothesize that the "inactive" X chromosome may show hormonally-driven, increased dynamism in the brain, with alterations in 3D structure, chromatin accessibility, and gene expression across the estrous cycle. To address this question, we combine the physiological C57/B6 mouse model with two genetic mouse models including female mice that have a mutation in the maternally-derived Xist allele (the Δ XistB6/Castaneus model) and females that are missing the inactive X chromosome (39, XO model). Ventral hippocampal neurons from control and mutant females during proestrus (high estradiol, low progesterone) and diestrus (low estradiol, high progesterone) phases of the estrous cycle, along with male controls, are analyzed using RNA-seq, ATAC-seq, and Hi-C to study gene expression, chromatin accessibility, and 3D genome organization, respectively (N=6 mice or 3 biological replicates/group/assay). Our findings demonstrate that 3D genome interactions dynamically change across the estrous cycle and sex, and suggest that the inactive X chromosome changes its compartmental organization, likely increasing in volume during the high estrogenic, proestrus stage of the cycle. We show estrous cycle-dependent changes in the expression of genes located in the X inactivation center (XIC) including the expression of the long non-coding RNA Xist, critical for the X chromosome inactivation. Finally, our results suggest that a subset of X-linked genes in ventral hippocampal neurons may escape inactivation in a cycle-dependent manner. These findings offer critical insights into sex-specific brain regulation, paving the way for sex-informed approaches to treating brain disorders, with significant implications for women's mental health.

Disclosures: L. Demarchi: None. A. Milosevic: None. D. Rocks: None. J. Rowley: None. M. Kundakovic: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.15/Q12

Topic: G.02. Neuroendocrine Processes and Behavior

Support: MEXT/JSPS KAKENHI Grant Number JP23H02362
MEXT/JSPS KAKENHI Grant Number JP21H05031
MEXT/JSPS KAKENHI Grant Number JP24K01905
Graduate Program of Transformative Chem-Bio Research at Nagoya University, supported by MEXT (WISE Program)
JST SPRING, Grant Number JPMJSP2125

Title: Possible involvement of cocaine- and amphetamine-regulated transcript neurons in lipopolysaccharide-induced suppression of luteinizing hormone secretion in female rats

Authors: *S. MATSUZAKI¹, Y. TOYOHAMA¹, K. YAMADA², N. INOUE¹, H. TSUKAMURA¹, Y. UENOYAMA¹;

¹Nagoya Univ. Grad. Sch. of Bioagricultural Sci., Nagoya-shi, Aichi, Japan; ²Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Reproductive function is orchestrated by the hypothalamus-pituitary-gonadal axis, in which kisspeptin neurons in the hypothalamic arcuate nucleus (ARC) serve as master regulators driving pulsatile gonadotropin-releasing hormone (GnRH)/gonadotropin secretion in mammals. Infectious diseases are known to attenuate reproductive function. Indeed, administration of lipopolysaccharide (LPS), an endotoxin, suppresses ARC kisspeptin gene (*Kiss1*) expression and luteinizing hormone (LH) secretion in female rats. This study aimed to identify neuropeptides involved in LPS-induced suppression of GnRH/gonadotropin secretion. We focused on an inhibitory neuropeptide, cocaine- and amphetamine-regulated transcript (CART, encoded by the *Cartpt* gene), as CART neurons reportedly project to ARC kisspeptin and GnRH neurons. We examined whether peripheral LPS administration activates hypothalamic CART neurons and whether central CART administration suppresses pulsatile LH secretion in female rats. Wistar-Imamichi female rats were ovariectomized (OVX) for 2 weeks. LPS was intravenously injected, and brains were collected 1 hour later for double *in situ* hybridization of *Cartpt* and *fos* mRNA (a marker of neuronal activation) expression in the hypothalamus. Another cohort of OVX rats were administered with CART into the third ventricle (3V) immediately after the first blood collection, and blood samples were collected every 6 min for 3 h from freely moving rats. Plasma LH concentrations were determined by radioimmunoassay, and the mean LH concentration, and the baseline, frequency, and amplitude of LH pulses were analyzed by the PULSAR computer program. Intravenous LPS administration significantly increased the percentage of fos-positive CART neurons in both the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN). In addition, 3V CART administration suppressed pulsatile LH secretion in OVX rats, and the mean LH concentration and the baseline and frequency of LH pulses were significantly lower in CART-treated OVX rats than in vehicle-treated control OVX rats. These findings suggest that CART neurons in the SON and PVN may mediate LPS-induced suppression of pulsatile GnRH/LH secretion, possibly via direct and/or indirect inhibition of ARC kisspeptin and/or GnRH neurons in female rats.

Disclosures: S. Matsuzaki: None. Y. Toyohama: None. K. Yamada: None. N. Inoue: None. H. Tsukamura: None. Y. Uenoyama: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.16/Q13

Topic: G.02. Neuroendocrine Processes and Behavior

Support: MEXT/JSPS KAKENHI Grant Number JP23H02362
MEXT/JSPS KAKENHI Grant Number JP21H05031
MEXT/JSPS KAKENHI Grant Number JP24K01905
MEXT/JSPS KAKENHI Grant Number JP24KJ1307

Title: Loss of DDX5 in the anteroventral periventricular nucleus kisspeptin neurons suppressed GnRH/LH surge and ovulation in female rats

Authors: *S. SEKI¹, S. HAZIM¹, R. ARIYOSHI¹, M. HIRABAYASHI², Y. UENOYAMA¹, H. TSUKAMURA¹, N. INOUE¹;

¹Nagoya Univ., Nagoya-shi, Aichi, Japan; ²Natl. Inst. for Physiological Sci., Okazaki, Aichi, Japan

Abstract: Hypothalamic kisspeptin neurons primarily control the release of gonadotropin-releasing hormone (GnRH) and play a pivotal role in the control of the hypothalamus-pituitary-gonadal axis in mammals. Specifically, kisspeptin neurons in the anteroventral periventricular nucleus (AVPV) are responsible for triggering GnRH/luteinizing hormone (LH) surge that leads to ovulation in rodents. This study aimed to identify transcriptional regulators that control *Kiss1* gene expression and neuronal activation of AVPV kisspeptin neurons. Our previous RNA-seq analysis using visualized kisspeptin neurons taken from *Kiss1*-tdTomato rats revealed the expression of DEAD-box helicase 5 (DDX5), which is known to regulate *c-fos* expression and to function as an estrogen receptor co-activator, in the *Kiss1*-tdTomato neurons. Double *in situ* hybridization for *Kiss1* and *Ddx5* in the AVPV of ovariectomized (OVX) wild-type rats primed with diestrous levels of estradiol-17 β (low E2) revealed that approximately 90% of AVPV *Kiss1*-expressing cells co-expressed *Ddx5*. Furthermore, specific knockdown of *Ddx5* in AVPV kisspeptin neurons—achieved by an injection of an adeno-associated (AAV) containing Cre-dependent *Ddx5* shRNA into the AVPV of *Kiss1*-Cre rats—significantly attenuated LH surge induced by preovulatory levels of E2 (high E2) in OVX *Kiss1*-Cre rats compared to those injected with AAV-negative-control shRNA. In ovary-intact *Kiss1*-Cre rats, AVPV kisspeptin neuron-specific *Ddx5* knockdown markedly reduced the amplitude of spontaneous LH surge and significantly decreased the number of ovulated oocytes. Moreover, the AVPV kisspeptin neuron-specific *Ddx5* knockdown tended to decrease the percentage of c-Fos-immunoreactive AVPV kisspeptin neurons, while it did not affect the number of *Kiss1*-expressing cells in the AVPV of OVX + high E2 *Kiss1*-Cre rats compared to control rats. Taken together, these findings suggest that DDX5 plays a critical role in the activation of AVPV kisspeptin neurons and the subsequent GnRH/LH surge and ovulation, without affecting AVPV *Kiss1* expression itself in these neurons.

Disclosures: S. Seki: None. S. Hazim: None. R. Ariyoshi: None. M. Hirabayashi: None. Y. Uenoyama: None. H. Tsukamura: None. N. Inoue: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.17/Q14

Topic: G.02. Neuroendocrine Processes and Behavior

Support: MEXT/JSPS KAKENHI Grant Number JP23H02362
MEXT/JSPS KAKENHI Grant Number JP21H05031
MEXT/JSPS KAKENHI Grant Number JP24K01905
Graduate Program of Transformative Chem-Bio Research at Nagoya University, supported by MEXT (WISE Program)
JST SPRING, Grant Number JPMJSP2125

Title: Cx3cr1 signaling mediates the suppression of luteinizing hormone secretion induced by lipopolysaccharides

Authors: *Y. OTSUKA, S. KADOI, K. YAMADA, Y. UENOYAMA, H. TSUKAMURA, N. INOUE;
Nagoya university, Nagoya, Japan

Abstract: The hypothalamic arcuate (ARC) kisspeptin neurons play as a master regulator for follicular development by controlling the pulsatile secretion of gonadotropin-releasing hormone (GnRH)/gonadotropin. Intracerebroventricular or peripheral administration of lipopolysaccharide (LPS) induces neuroinflammation by activating glial cells in the brain and suppresses luteinizing hormone (LH) pulses. We found that an inhibitory G protein-coupled receptor (GPCR), CX3CR1, which has been reported to be involved in immune responses during neuroinflammation, is highly expressed in the ARC region in female rats. The present study, therefore, aims to determine whether CX3CR1 signaling mediates the LPS-induced suppression of pulsatile LH secretion in ovariectomized rats treated with a negative feedback level of estradiol-17 β (OVX + low E2). Wistar-Imamichi female rats were used. A CX3CR1 antagonist (AZD8797) or 50% dimethyl sulfoxide (50% DMSO, as a vehicle) was administered into the third ventricle (3V) of the OVX + low E2 rats, followed by intravenous (iv) administration of LPS or saline. Plasma samples were taken at 6-minute intervals for 3 hours immediately after 3V AZD8797 administration, and plasma LH levels were measured by radioimmunoassay. Pulsatile LH secretion was markedly suppressed by iv LPS administration in the 3V DMSO-injected group, whereas LH pulses were observed in some iv LPS-treated rats pretreated with 3V AZD8797. The mean LH concentration, and baseline and amplitude of the LH pulse were significantly higher in the 3V AZD8797-iv LPS-treated group compared to the 3V DMSO-iv LPS-treated group. LH pulse frequency tended to be higher in the 3V AZD8797-iv LPS-treated group compared to 3V DMSO-iv LPS-treated group. Double *in situ* hybridization for the kisspeptin gene (*Kiss1*) and CX3CR1 gene (*Cx3cr1*) revealed that both *Cx3cr1*-expressing cells and *Kiss1*-expressing cells were present in the ARC of OVX + low E2 rats, while only a small subset of *Kiss1*-expressing cells co-expressed *Cx3cr1*. These findings suggest that the iv LPS-induced suppression of LH pulses is, at least in part, mediated by CX3CR1 signaling through an indirect effect on ARC kisspeptin neurons.

Disclosures: Y. Otsuka: None. S. Kadoi: None. K. Yamada: None. Y. Uenoyama: None. H. Tsukamura: None. N. Inoue: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.18/Q15

Topic: G.02. Neuroendocrine Processes and Behavior

Title: Menopausal Status and Hormone Therapy Influence Brain Volume in Females with Traumatic Brain Injury

Authors: *G. ESPAÑA IRLA, E. M. TINNEY, T. P. MORRIS;
Northeastern Univ., Boston, MA

Abstract: Traumatic brain injury (TBI) is increasingly recognized as a risk factor for later-life cognitive decline, yet its long-term effects may vary depending on the timing of injury relative to key hormonal transitions in females. Given the neuroprotective properties of oestrogen, menopause may be a critical modifier of TBI-related brain changes and recovery. In this study, we investigated whether hormonal status at the time of injury—specifically, premenopausal vs. postmenopausal—was associated with differential structural brain volume in females. We also examined whether hormone replacement therapy (HRT) influenced these structural brain volumes in postmenopausal females with TBI. Structural MRI and demographic data were obtained from the UK Biobank, a large population-based cohort of middle- to older-aged females. Participants were grouped for Analysis 1 (TBI premenopausal [n=30], TBI postmenopausal [n=49], healthy controls [n=69]) and Analysis 2 (TBI postmenopausal with HRT [n=188], without HRT [n=254], healthy controls with HRT [n=135], without HRT [n=224]). ANCOVA was used to assess group differences in grey matter volumes, adjusting for age, education, waist circumference, number of births, and reproductive span. In Analysis 1, significant group differences were found in the superior frontal gyrus grey matter volume ($F = 3.09$, $p = 0.049$), indicating localized structural alterations associated with TBI timing. In Analysis 2, both healthy HRT users and TBI participants who used HRT showed significantly lower global grey matter volume compared to healthy non-users ($F = 6.15$, $p < 0.001$). These findings underscore the importance of hormonal status in evaluating the long-term neural impact of TBI in females. The observed structural differences point to complex interactions between injury, aging, and endocrine factors, highlighting the need for further research into hormone-related neurobiological mechanisms after TBI.

Disclosures: G. España Irla: None. E.M. Tinney: None. T.P. Morris: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.19/Q16

Topic: G.02. Neuroendocrine Processes and Behavior

Support: EMBO Scientific Exchange Grant 11051

Title: Unraveling changes in the brain's connectome during the transition to motherhood

Authors: *C. SERVIN-BARTHET^{1,3}, M. PATERNINA-DIE^{4,5,7}, M. MARTÍNEZ-GARCÍA⁸, D. MARTIN DE BLAS^{4,6,7}, C. SEGUIN⁹, Y. TIAN⁹, A. ZALESKY¹⁰, S. CARMONA¹¹, O. VILARROYA^{1,2};

¹Psychiatry and Legal Med., ²Univ. Autònoma de Barcelona, Barcelona, Spain; ³Hosp. del Mar Res. Inst., Barcelona, Spain; ⁴Inst. de Investigación Sanitaria Gregorio Marañón, Madrid, Madrid, Spain; ⁶Dept. de Bioingeniería, ⁵Univ. Carlos III de Madrid, Madrid, Spain; ⁷CIBER de Salud Mental, Madrid, Spain; ⁸Dept. of Psychological and Brain Sciences, Univ. of California Santa Barbara, Santa Barbara, CA; ⁹Univ. of Melbourne, Melbourne, Australia; ¹⁰Melbourne Neuropsychiatry Ctr., Melbourne, Australia; ¹¹Hosp. Gen. Gregorio Marañón, Madrid, Spain

Abstract: Growing evidence suggests that pregnancy leads to a reorganization of brain neuroanatomy that may help the mother-to-be cope with the challenges of motherhood. Beyond the observed neuroanatomical changes, the remodeling of the mother's connectome remains largely unexplored. This study investigated changes in the maternal connectome during the transition to motherhood, using prospective and longitudinal MRI data from 148 first-time mothers and 48 nulliparous controls. First-time mothers were scanned at three points: pre-conception, one month postpartum, and six months postpartum. Nulliparous women were scanned at matched intervals to control changes unrelated to motherhood. Four diffusion-weighted imaging metrics were analyzed using tract-based spatial statistics to characterize changes in white matter microstructure. Nonparametric permutation testing (5,000 permutations) and Bonferroni-corrected thresholds ($p = 0.0125$) were applied to ensure robust inference. Results revealed that relative to controls, gestational mothers exhibited a significant decrease in fractional anisotropy in the right forceps minor from pre-conception to one month postpartum (Group x Session interaction [1 month postpartum]: $B = -1.41e-02$, t value = -5.32 , $p < 0.001$). Concurrently, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) significantly increased in the bilateral fornix and thalamic radiations (MD: Group x Session interaction [1 month postpartum]: $B = 6.77e-05$, t -value = 6.57 , $p < 0.001$; RD: Group x Session interaction [1 month postpartum]: $B = -6.38e-05$, t value = 6.62 , $p < 0.001$; AD: Group x Session interaction [1 month postpartum]: $B = 7.76e-05$, t value = 6.51 , $p < 0.001$). All changes normalized by six months postpartum. These findings suggest transient white matter remodeling associated with early motherhood, highlighting the maternal brain's plasticity, specifically in regions implicated in social cognition, memory, and emotional regulation.

Disclosures: C. Servin-Barthet: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.20/R1

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIMH T32
BBRF Grant

Title: Longitudinal Characterization of Maternal EEG Across the Perinatal Period

Authors: *M. S. ATTRE, A. LEOW, B. PEÑALVER BERNABÉ;
Univ. of Illinois Chicago, Chicago, IL

Abstract: The perinatal period is highly dynamic with hormonal, mood, and neural fluctuations varying amongst individuals across gestational weeks (GWs) and up to one year postpartum. Widespread, structural brain changes have been linked to normal pregnancy. However, functional characterization of the perinatal brain remains limited, especially longitudinally. We aim to investigate how brain electrical activity may alter longitudinally across pregnancy and postpartum using portable electroencephalography (pEEG). Participants (n=80, 46% Black, 39% Hispanic, 56% on Medicaid) completed resting state EEGs at five time points across the perinatal period: <16 gestational weeks (n=41), 20 gestational weeks (n=30), 24-28 gestational weeks (n=44), 36 gestational weeks (n=33) and 6 weeks postpartum (n=30). The relative power of alpha, beta, delta, theta, and gamma bands was determined. Linear regression and linear mixed-effect models were used to identify the association between spectral power for each waveform and progression through pregnancy as marked by estimated gestational age (EGA) in days or days since delivery for the postpartum period. Models used by participant mental health severity, race, ethnicity, socioeconomic status, and enrollment gestational age as covariates. We found four associations between frequency-band waveform power and estimated gestational age (EGA). Beta and gamma waves significantly positively associated with EGA during the overall perinatal period ($p=0.01$ and $p=0.02$, respectively). This association strengthened specifically in the antenatal period alone ($p = 0.005$ and $p = 0.007$, respectively). Over the overall perinatal period, theta waves significantly positively associated with EGA ($p= 0.04$), whereas alpha waves significantly negatively associated with EGA ($p = 0.01$). We also completed connectivity analysis to explore the resting state connections across electrodes. This study is one of the first to assess electroencephalographic changes in brain activity from early pregnancy through postpartum across eighty individuals. Two patterns of electroencephalographic changes associated with EGA: two wave changes (increased beta and gamma waves) most specific to the antenatal period, and two wave changes (increased theta and decreased alpha waves) specific to the entire perinatal period. These two specific patterns imply there may be (i) gestational-specific neurological adaptations, which may reflect hormonal and other gestational-related changes, as well as (ii) potentially longer-term perinatal neurological adaptations, which reflect widespread, persistent neurological reorganization.

Disclosures: M.S. Attre: None. A. Leow: None. B. Peñalver Bernabé: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.21/R2

Topic: G.02. Neuroendocrine Processes and Behavior

Title: Inducible reporter assays for functional characterization of neurological drug candidates

Authors: H. TANG, E. GREENE, V. SAPP, J. BILAKOVICS, *A. YEHIA, V. BARON, **J. PARK;**
BPS Biosci., San Diego, CA

Abstract: The discovery and development of therapeutics for neurological and neuropsychiatric disorders requires the development of specialized models enabling the evaluation of agonistic or antagonistic effects of candidate compounds. Cell-based assays have become an essential tool in the drug development process, providing researchers with the ability to evaluate biological activities and interferences of potential drug candidates otherwise hidden in cell-free biochemical assays. By integrating luciferase reporters downstream of pathway-specific promoter elements, these innovative cellular models enable straightforward, quantitative, and highly sensitive detection of receptor activation. Hence, we developed a series of cell lines to simplify interrogation of various receptor-signaling pathways for drug screening and characterization. These cells respond to agonists by displaying a dose-dependent increase in luciferase activity. Examples of these are Muscarinic Acetylcholine Receptor NFAT Luciferase reporter cell lines generated by expressing mAChR M1, M3 or M5, together with a firefly luciferase reporter under the control of an NFAT (nuclear factor of activated T cells) response element. Similarly, GLP-1R (Glucagon-like peptide 1 receptor), GIPR (gastric inhibitory peptide receptor), or Glucagon Receptor (GCGR) expressed together with a luciferase reporter under the control of cAMP response elements (CRE). In addition, we were successful in building cell lines expressing hybrid constructs of human thyroid receptor α or β ligand binding domain fused to the DNA binding domain of GAL4, together with firefly luciferase reporter under the control of the GAL4 upstream activation sequence (UAS). The resulting systems can specifically detect thyroid hormone-induced activation of the receptor with low cross-reactivity from other nuclear receptors. For each cell line, functionality was validated by measuring the IC₅₀ of various agonists or new therapeutics. Thus, inducible reporter assays are an ideal option to study effectors of cell signaling pathways in the context of intact functioning cells. Luciferase reporters downstream of a pathway-specific promoter response element allow simple, robust, and quantitative measurement of signaling activity.

Disclosures: H. Tang: None. E. Greene: None. V. Sapp: None. J. Bilakovics: None. A. Yehia: None. V. baron: None. J. Park: None.

Poster

PSTR030: Hormones and Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR030.22/R3

Topic: G.02. Neuroendocrine Processes and Behavior

Support: KAKENHI 23K10598

Title: Effects of Vertical vs. Horizontal Space Expansion in Enriched Environments on Physical Activity and Monoamine Levels in Rats

Authors: *S. YANAGITA¹, N. KUBOTA²;

¹Tokyo Univ. of Sci., Chiba, Japan; ²Sch. of Human and Social Sci., Tokyo Intl. Univ., Saitama, Japan

Abstract: Enriched environments (EEs) are widely used in rodent models to enhance neuroplasticity and behavioral adaptation, often through the activation of central monoaminergic systems such as dopamine and serotonin. These neurobiological effects are frequently attributed to increased physical activity levels. However, previous studies have primarily focused on two-dimensional spatial expansion, and the effects of spatial orientation—vertical versus horizontal—on brain and physical function remain unclear. This study aimed to investigate whether the direction of spatial expansion in EEs influences spontaneous physical activity, brain monoamine levels, and peripheral physiological changes in rats. Male Wistar rats were randomly assigned to two housing conditions for four weeks: a Multistory Enriched Environment (MEE) or a Wide Enriched Environment (WEE). Both environments had the same total area but differed in orientation. The MEE consisted of three vertically stacked levels connected by ramps to promote climbing and vertical movement. The WEE expanded the same area horizontally, without elevation. Physical activity was recorded continuously using mobile accelerometers. After four weeks, brain monoamine concentrations and their metabolites were measured via high-performance liquid chromatography (HPLC) in the prefrontal cortex, hippocampus, striatum, and midbrain. Additionally, skeletal muscle and fat tissue were dissected and weighed post-mortem. The MEE group exhibited more complex locomotor patterns, including vertical movement, but showed no significant increase in total physical activity compared to the WEE group. The MEE group also showed more irregular diurnal activity patterns, suggesting different circadian engagement. No statistically significant differences were found in brain monoamine or metabolite concentrations between MEE and WEE. However, the MEE group showed significantly increased muscle mass in anti-gravity muscles, particularly the soleus, indicating that vertical activity may lead to localized mechanical loading and muscle development. These results suggest that while vertical space expansion changes the quality and structure of movement, it does not necessarily lead to greater activity volume or enhanced monoaminergic activity. The pattern and functional type of movement may play a more critical role in neurochemical modulation than movement quantity alone. In conclusion, spatial orientation in enriched environments can lead to different physical adaptations, particularly in skeletal muscle, without significant impact on brain monoamine systems.

Disclosures: S. Yanagita: None. N. Kubota: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.01/R4

Topic: G.03. Stress and the Brain

Support: DBT-Wellcome Trust India Alliance Intermediate Fellowship Grant
IA/CPHI/18/1/503964)

Title: Early-pregnancy DNA methylation signatures predict risk of antenatal depression: an epigenome-wide association study

Authors: *K. GOKULAKRISHNAN¹, T. CHINNASAMY³, K. SHARMA⁴, M. DEEPA⁵, B. SRIKUMAR², U. RAM⁶, A. RANJIT MOHAN⁵, M. BALASUBRAMANYAM⁵, V. MOHAN⁵, P. SARAVANAN⁷;

²Neurophysiol., ¹Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India;

³Natl. Inst. of Mental Hlth. and Neuro Sci., BANGALORE, India; ⁴Natl. Inst. of Mental Hlth. & Neuro Sci., BANGALORE, India; ⁵Madras Diabetes Res. Fndn., Chennai, India; ⁶Seethapathy Clin. & Hosp., Chennai, India; ⁷Populations, Evidence and Technologies, Div. of Hlth. Sciences, Warwick Med. School, Univ. of Warwick, Coventry, United Kingdom

Abstract: Background and aim: Depression during pregnancy is associated with adverse maternal and child outcomes, but the underlying biological mechanisms remain poorly understood. DNA methylation, an epigenetic modification responsive to endogenous and environmental stressors, may mediate these effects. We therefore aimed to study whether DNA methylation signatures in early pregnancy can predict the later onset of antenatal depression.

Methods: In this nested case-control study, 189 pregnant women (12-16 weeks of gestation) without a prior history of depressive symptoms and with PHQ-9 scores (<4) were recruited from the Stratification of Risk of Diabetes in Early Pregnancy study (STRiDE) cohort. Depressive symptoms were assessed at 24-28 weeks using the PHQ-9, and 93 women were identified as depressed and 96 as non-depressed. DNA methylation profiling was performed using the Illumina EPIC BeadChip array. After quality control, 596,418 CpG sites were included in the epigenome-wide association study (EWAS) data analysis, adjusting for maternal age, BMI, gestational age, GDM, parity, and infant sex. **Results:** EWAS identified 697 differentially methylated CpGs significantly associated with antenatal depression (FDR < 0.05). A random forest classifier identified a panel of 5 CpGs cg05348295 (FAM129B), cg14473743 (NUP210), cg08825190 (RAB3A), cg23543263 (FGF9), and cg15872575 (ASB18) robustly predicted the onset of depression during 24-28 weeks of pregnancy with an AUC of 0.98 in the test and 0.85 in bootstrap validation datasets, with 77% sensitivity and 75% specificity. Interestingly, all 5 CpGs were hypomethylated, showed significant correlation with PHQ-9 scores and implicated in neuropsychiatric disorders. Pathway enrichment analysis revealed involvement in circadian

entrainment, dopaminergic synapse, and oxytocin signalling pathways. **Conclusion:** Our study identified a panel of 5 DNA methylation signatures in early pregnancy that could potentially predict the development of antenatal depression at 24-28 weeks. These findings support the utility of epigenetic signatures in early screening, enabling timely interventions (behavioural counselling) to reduce long-term risks for both mother and child, and contribute to the development of precision medicine approaches in perinatal mental health.

Disclosures: K. Gokulakrishnan: None. T. Chinnasamy: None. K. Sharma: None. M. Deepa: None. B. Srikumar: None. U. Ram: None. A. Ranjit Mohan: None. M. Balasubramanyam: None. V. Mohan: None. P. Saravanan: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.02/R5

Topic: G.03. Stress and the Brain

Support: Boehringer Ingelheim Fonds PhD Fellowship
NIMH
Hope for Depression Research Foundation

Title: Gene regulation by ovarian hormone receptors contributes to sex differences in stress-induced transcriptional profiles

Authors: *C. A. MCLAIN¹, A. CUNNINGHAM³, M. ESTILL¹, T. M. GYLES⁶, L. HOLT⁴, O. ISSLER⁵, V. KONDEV¹, G. ROJAS², E. J. NESTLER⁷;
²Nash Family Dept. of Neurosci. and Friedman Brain Inst., ¹Icahn Sch. of Med. at Mount Sinai, New York, NY; ⁴Neurosci. Dept., ⁵Neurosci., ³Mount Sinai Sch. of Med., New York, NY;
⁶Friedman Brain Inst., ⁷Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Chronic stress produces sex-specific neurobiological and behavioral outcomes which are associated with greater stress susceptibility in female animals and a higher prevalence of depression in women. Our understanding of the molecular mechanisms driving sex-differentiated stress responses is limited. To address this, we used the four core genotypes mouse model - in which sex chromosomes are dissociated from gonadal sex by expressing the *Sry* gene autosomally - to determine the relative contributions of hormonal versus chromosomal factors. Our findings indicate that hormonal sex plays the dominant role in driving both behavioral and transcriptional responses to chronic stress, while also identifying a weaker contribution of the X and Y chromosomes. As such, we utilized CUT&RUN to investigate the role of sex hormone receptors as transcription factors in stress-responsive brain regions. Here, we map the genome-wide binding sites of estrogen and progesterone receptors in multiple regions under both baseline and stress conditions. We characterize region-, sex-, and estrous-stage specific binding patterns, and highlight the ways in which stress alters the regulatory functions of these receptors. Finally,

we identify a set of genes, and functional processes, consistently regulated by both ovarian hormones and stress across datasets. These experiments aim to define the molecular basis of the dramatic sex differences seen in chronically stressed rodents and in depressed humans, which will help define sex-specific approaches for novel therapeutics for human stress disorders.

Disclosures: C.A. McLain: None. A. Cunningham: None. M. Estill: None. T.M. Gyles: None. L. Holt: None. O. Issler: None. V. Kondev: None. G. Rojas: None. E.J. Nestler: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.03/R6

Topic: H.05. Mood Disorders

Support: UWM

Title: The Role of Estrogen Receptor Beta in Stress-Induced Sleep Disturbances and Maladaptive Behavioral Responses in Mice

Authors: *G. PANDYA¹, S. ZIMMERMAN², P. GEORGIU²;

¹Univ. of Wisconsin - Milwaukee, Milwaukee, WI; ²Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Depression is a prevalent mental health disorder impacting daily functioning and quality of life. Sleep and circadian disturbances are both symptoms and contributing factors in the etiology and progression of depression. Circadian cycle changes (i.e., shift work) and poor sleep quality sleep are linked to more severe depressive symptoms, reduced treatment responsiveness, and higher relapse rates. Understanding how sleep and circadian cycles affect depression may unveil potential therapeutic targets. One possible mechanism for these impairments may be dysregulation of estrogen receptor beta (ER β). We hypothesized that reduced hedonic response following stress is due to the shift in circadian rhythmicity and sleep architecture impairments, an effect that is regulated by ER β . Hence, we measured hedonic responding in male and female mice for consecutive 24-hour circadian cycles at baseline, after gonadectomies (i.e., estradiol elimination), post-acute stress tests, and after re-exposure to the stressful environment, using operant conditioning with a fixed ratio 1 schedule of reinforcement. Also, using telemetry, we measured sleep patterns in ER β knockout mice at baseline and following acute stress. Mice were treated with the ER β agonist, DPN, or vehicle 30 min prior to stress exposure. Male and female mice demonstrated normal circadian patterns of responding with higher nose pokes during their active period. Male mice had increased responding in both the active and inactive holes following gonadectomy, an effect that was decreasing following stress and reversed by DPN. In female mice, decreased impulsivity as measured by premature responses was found after gonadectomy. No differences were observed in responding between baseline and post-gonadectomy. Notably, female DPN treated mice demonstrated increased

responding following stress and showed prophylactic effects against restress where control mice showed a significant decrease in active responding. Importantly, a possible shift in circadian pattern rhythmicity may be present with shifts towards higher responding activity levels during their inactive period, an effect attenuated by DPN. In addition, we observed increased rapid-eye movement sleep during the daytime in ER β knockout mice following acute stress, accompanied by a simultaneous decrease in sucrose preference. Additionally, the sleep impairments were accompanied by an increase in delta and gamma power during the day in ER β knockout mice. These results suggest that dysregulation of E2/ER β system may underlie sleep, circadian, and hedonic impairments following acute stress, and ER β activation may play neuroprotective role.

Disclosures: G. Pandya: None. S. Zimmerman: None. P. Georgiou: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.04/R7

Topic: G.03. Stress and the Brain

Support: NSF Grant 2441642
ORAU Ralph E Powe Junior Faculty Enhancement Award
Good Nature Institute
Utah State University Office of Research

Title: Assessing the grieving brain: Effect of partner loss on oxytocin, vasopressin, corticotropin releasing hormone, and opioid receptor systems of the monogamous coyote brain

Authors: R. R. ROWE¹, R. TONG¹, B. NIELSON¹, K. KELLER¹, J. HOPKIN¹, D. RANGLACK², *S. M. FREEMAN¹;

¹Biol., Utah State Univ., Logan, UT; ²Wildlife Services, USDA, Millville, UT

Abstract: Social relationships are critical not only to human well-being but are evident throughout the animal kingdom. Selective mating among monogamous rodents and non-human primates have largely provided the model species to understand the biology of bond formation and the effect of partner loss. There has been no social bonding work done on canids such as coyotes (*Canis latrans*), which display mating exclusivity and genetic monogamy. Partner loss can provide devastating, life altering effects in humans, and neuroscience research has implicated the involvement of the neuropeptides oxytocin (OXT) and vasopressin (AVP), the stress system (specifically corticotropin releasing hormone (CRH)), and the endogenous opioid reward system in the neurobiology of social bond loss. Ongoing research in our lab has aimed to quantify the grieving brain through the study of postmortem tissue from adult coyotes. We opportunistically acquired coyote brains from animals housed at the USDA National Wildlife Research Center's Predator Research Field Station in Millville UT. Brains from 3 widowed females and 4 paired females were extracted within 2-3 hours after euthanasia, cryosectioned at 20 μ m, thaw mounted

to microscope slides, and frozen until use in assays. Using previously published methods, we performed quantitative receptor autoradiography with selective radioligands on adjacent series of brain sections to assess the effect of partner loss on: OT receptors (OXTR), AVP 1a receptors (AVPR1a), CRH receptor subtypes 1 (CRHR1) and 2 (CRHR2), mu opioid receptors (MOR), and kappa opioid receptors (KOR). We found no significant mean differences between paired and widowed females for OXTR binding in forebrain regions, but there were significant differences in the variance around the mean in the nucleus accumbens and lateral septum, potentially indicating a shunting of the plasticity in OXTR expression in those areas. We also found a trend toward reduced OXTR binding in the hippocampus in widows, a pattern that was not seen in adjacent midbrain regions. There were no significant differences in AVPR1a binding, but we did find an increase in CRHR1 and CRHR2 in olfactory and memory areas, potentially indicating a sensitization to incoming olfactory social stimuli after partner loss. Ongoing research is evaluating mu and kappa opioid receptor densities, which will contribute to this larger assessment of the effects of social bond loss on neuropeptide receptor levels in the monogamous brain. This work has implications for lethal management of coyotes and may provide translational context as it relates to the loss of a dog-owner bond in dogs.

Disclosures: R.R. Rowe: None. R. Tong: None. B. Nielson: None. K. Keller: None. J. Hopkin: None. D. Ranglack: None. S.M. Freeman: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.05/R8

Topic: G.03. Stress and the Brain

Support: MH125408

Title: Behavioral alterations associated with partner loss and isolation in female prairie voles

Authors: *A. AKBARABADI¹, F. DUCLOT², Y. LIU³, Z.-X. WANG⁴, M. KABBAJ²;
²Biomed. Sci., ³Psychology, ⁴Psychology & Neurosci., ¹Florida State Univ., Tallahassee, FL

Abstract: Social affiliation is a core characteristic of human social behaviors. While enduring social attachments promote human health and well-being, their sudden loss experienced during complex grief or bereavement can also foster many aspects of mental disorders. Despite extensive empirical evidence linking partner loss and mental health in humans, the underlying neurochemical mechanisms remain unclear due to a lack of appropriate animal models. The prairie vole (*Microtus ochrogaster*) is a socially monogamous rodent that forms enduring social attachments—preferring their partner over strangers and displaying selective aggression towards unfamiliar conspecifics—and therefore represents an excellent opportunity to elucidate the consequences of partner loss. This study aimed at determining the behavioral consequences of partner loss in prairie voles. Adult female prairie voles were first cohabitated with a male for 48

hrs or 2 weeks—both known to reliably establish a bond—before being separated or left with their male partner for the remainder of the study. Following at least 10 days of separation/non-separation and verification of the presence of the pair-bond with a partner preference test, all females underwent a battery of behavioral tests to measure avoidance behaviors in an elevated plus maze, sociability, social discrimination, selective aggression, as well as development, extinction, and reinstatement of a conditioned place preference to D-amphetamine. Notably, to distinguish the effects of partner loss itself from its inherent social isolation, parallel groups of females remained in same-sex pairs (grouped) or isolated for the same duration. Overall, despite a continued partner preference, separated females showed reduced selective aggression when compared to non-separated controls independent from potentially confounding deficits in social recognition. Notably, such effects were not observed following isolation alone, indicating their specificity to partner loss. All groups developed a CPP to D-AMPH, however, suggesting a conserved response of the mesolimbic dopamine system following partner loss/isolation. Altogether, this study describes a pattern of alterations in social behaviors following partner loss in female prairie voles distinguished from the effects of social isolation itself, allowing for a targeted, further functional deciphering of their underlying neurobiology.

Disclosures: A. Akbarabadi: None. F. Duclot: None. Y. Liu: None. Z. Wang: None. M. Kabbaj: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.06/R9

Topic: G.03. Stress and the Brain

Support: JSPS Grant JP20H03353
JSPS Grant JP20J21209
JSPS Grant JP20K21456
MEXT Grant JP21H00199
AMED Grant JP19gm1110008
AMED Grant JP21wm0425018

Title: Neural basis of individual behavioral outcomes triggered by chronic social defeat stress in mice

Authors: *H. OKAMURA^{1,2}, S. YASUGAKI^{1,3}, H. SUZUKI-ABE¹, Z. WANG⁴, Y. ARAI^{1,3}, M. YANAGISAWA¹, H. TAKIZAWA^{5,6}, Y. HAYASHI^{1,3};

¹WPI-IIIS, Univ. of Tsukuba, Tsukuba, Japan; ²Ph. D. Program in Humanics, Univ. of Tsukuba, Tsukuba, Japan; ³Dept. of Biol. Sciences, Grad. Sch. of Science, Univ. of Tokyo, Tokyo, Japan;

⁴Master's Program in Computer Science, Univ. of Tsukuba, Tsukuba, Japan; ⁵Inst. of Systems and Information Engineering, Univ. of Tsukuba, Tsukuba, Japan; ⁶Academic Computing and Communications Center, Univ. of Tsukuba, Tsukuba, Japan

Abstract: Stress resilience varies greatly among individuals. For those who are vulnerable to stress, they have a heightened risk of developing mental disorders such as depression when they are exposed to social stress. Mice show similar outcomes: even though they have identical genetic background, social stress can elicit various extent of behavioral changes. The underlying biological mechanisms that decide resilience or susceptibility remains poorly understood. To clarify the mechanisms, we exposed BALB/c mice to chronic social-defeat stress (SDS) and tracked their long-term effects on behavior. The social avoidance after the exposure of chronic SDS was investigated and roughly half of the defeated mice exhibited social avoidance, whereas the rest remained sociable (Okamura et al., eNeuro, 2022). Notably, within the two-week interval after the stress exposure period, some mice switched phenotypes, from avoidant to non-avoidant (or vice versa). Next, we tried to find brain regions that differentiate (i) defeated from naïve mice and (ii) avoidant from non-avoidant subgroups during social interaction. c-Fos expression was used as an indicator of neuronal activation. Using the semi-automatic whole-brain c-Fos mapping technique we had developed previously, we identified several brain regions with altered c-Fos densities in defeated mice compared to naïve mice. Among these, especially, the lateral habenula (LHb) was prominent. Mice that were avoidant immediately after SDS showed different LHb c-Fos signal density compared to those that became avoidant only at later social interaction. Furthermore, based on this semi-automatic c-Fos mapping technique, we have now created a high-throughput workflow incorporating convolutional neural networks (CNNs), which enables a novel method for extracting c-Fos-positive cells by simultaneously capturing local detailed features and broader spatial distribution patterns. Together, these results contribute to understanding neural mechanisms that govern individual differences in stress resilience and paving the way for even larger-scale brain-wide analyses in future studies.

Disclosures: **H. Okamura:** None. **S. Yasugaki:** None. **H. Suzuki-Abe:** A. Employment/Salary (full or part-time): Currently an employee of Astellas pharma (all works were completed before being the employee). **Z. Wang:** None. **Y. Arai:** None. **M. Yanagisawa:** None. **H. Takizawa:** None. **Y. Hayashi:** None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.07/R10

Topic: G.03. Stress and the Brain

Support: Huck Institutes of the Life Sciences

Title: Hypothalamic and hippocampal gene expression associated with stable behavioral traits and stress hormone regulation

Authors: ***I. MARTINI BERNARDI**¹, **E. COVER**³, **S. FARHAN**⁴, **E. K. MCMAHON**⁵, **S. A. CAVIGELLI**²;

¹Psychology, Penn State Univ., State College, PA; ²Biobehavioral Hlth., Penn State Univ.,

University Park, PA; ³Biol. Engin., MIT, Cambridge, MA; ⁴Sidney Kimmel Med. Col., Thomas Jefferson Univ., Philadelphia, PA; ⁵Sch. of Med. & Hlth. Sci., George Washington Univ., Washington, DC

Abstract: Stress exposure activates many physiological pathways that can influence behavior. One of the central stress response systems is the hypothalamic-pituitary-adrenal (HPA) axis which is responsible for maintaining homeostasis and is associated with glucocorticoid synthesis, a steroid hormone secreted by the adrenal glands and regulated by corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH). When chronically activated, this response leads to over-synthesis of glucocorticoids that can have negative impacts on health, including maladaptive behaviors related to fear, memory, and anxiety. The adenylate cyclase activating polypeptide 1 (ADCYAP1) gene encodes for the pituitary adenylate cyclase-activating polypeptide (PACAP) which is found in stress-associated brain regions. This gene is reported to upregulate CRH expression in the paraventricular nucleus of the hypothalamus and to be associated with altered stress/anxiety-related behaviors (exploratory, fear extinction/discrimination, reward-seeking behaviors) when upregulated in the bed nucleus of the stria terminalis and the dentate gyrus in the hippocampus. Chronic exposure to stress can lead to higher activation of ADCYAP1 in both structures, leading to higher synthesis/secretion of CRH and glucocorticoids and failure to return to homeostasis, which can have negative health and behavioral consequences. In this observational study, we investigated whether consistent behavioral traits (i.e. temperaments) previously associated with glucocorticoid secretion are associated with altered hypothalamic or hippocampal basal expression of ADCYAP1 and other HPA-regulation genes. In 54 outbred adult Sprague Dawley male rats we quantified multiple temperaments and brain gene expression. Temperament was characterized based on rat responses to 5 different behavioral tests, each conducted three times. RT-PCR was used to measure mRNA levels of ADCYAP1, Glucocorticoid Receptor (GR), and FKBP5 (a negative regulator of GR). Results showed decreased hippocampal ADCYAP1 and FKBP5 expression in a stable temperament associated with decreased glucocorticoid reactivity: Social Boldness ($r=-0.313$ and -0.266). Hippocampal FKBP5 expression was also positively correlated with glucocorticoid reactivity to stress ($r=0.363$). However, hypothalamic gene expression was not related to glucocorticoid-related temperaments. These results suggest that naturally occurring temperaments and their associated stress physiology are associated with altered hippocampal basal expression of genes but not hypothalamic expression.

Disclosures: I. Martini Bernardi: None. E. Cover: None. S. Farhan: None. E.K. McMahon: None. S.A. Cavigelli: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.08/R11

Topic: G.03. Stress and the Brain

Support: NIDA INVEST Post-Doctoral Fellowship

Title: Sex-specific neurochemical remodeling of Lateral Hypothalamic Perineuronal Nets following olfactory-conditioned stress: Behavioral and structural evidence

Authors: *N. BOUHADDOU^{1,2}, B. N. KUHN², R. HODEBOURG², P. W. KALIVAS²;
¹Fac. of Sci. - Mohammed V Univ. in Rabat, Rabat, Morocco; ²Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: The neurochemical mechanisms underlying stress memory consolidation remain incompletely understood, particularly regarding sex-specific adaptations in extracellular matrix plasticity. Perineuronal nets (PNNs), regulators of synaptic stability, may mediate stress-induced behavioral phenotypes. We investigated sex-dependent alterations in defensive behaviors and PNN density within the lateral hypothalamus (LH) following olfactory-paired restraint stress in rats. Adult male and female Long-Evans rats (n=10 per group) underwent two 2-hour restraint sessions paired with essential oil exposure (conditioned), restraint without odor pairing (neutral), or odor exposure without restraint (control). Following 21-day consolidation, animals were re-exposed to the conditioned odor. Behavioral assessments included freezing, stress zone occupancy, defensive burying, and grooming frequency. Plasma corticosterone was measured and PNN density was quantified in LH subregions using Wisteria floribunda agglutinin and confocal microscopy. Conditioned females demonstrated higher freezing responses compared to males (0.4% vs 0.2%). Stress zone occupancy showed treatment and sex effects with higher occupancy observed in conditioned animals vs. controls, and in males vs. females (conditioned males: ~17% vs conditioned females: ~12%). When normalized to habituation baseline, freezing ratios showed no significant differences across groups or sexes. However, neutral females demonstrated elevated stress zone occupancy ratios compared to both control and conditioned females. PNN density analysis in males revealed increased PNN density in conditioned animals compared to neutral and control groups. PNN analysis in females is currently in progress. Our findings demonstrate sex-specific behavioral adaptations to olfactory-conditioned stress. Males showed higher stress zone occupancy following conditioning, while females exhibited higher freezing responses, suggesting sex-dependent defensive strategies. Preliminary neurochemical analysis revealed increased PNN density in conditioned males, suggesting extracellular matrix remodeling as a potential mechanism underlying male stress adaptation. These results underscore the complexity of sex-dependent stress responses and the role of the LH in behavioral and neurochemical adaptations.

Disclosures: N. Bouhaddou: None. B.N. Kuhn: None. R. Hodebourg: None. P.W. Kalivas: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.09/R12

Topic: G.03. Stress and the Brain

Support: 1R01HL173525
1F32HL172693

Title: Synaptic, neurochemical, and anatomical properties of the medial prefrontal cortex-posterior hypothalamic circuit

Authors: *C. A. BOUCHET, E. C. PINSINSKI, J. C. COOK, F. R. STOCKLEY, C. E. VAAGA, B. MYERS;
Dept. of Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Top down signaling from the cortex to the hypothalamus is critical to link cognitive and emotional processing to homeostasis and motivation. Historically, the neurobiological mechanisms underlying the relationships between behavior and physiology have only been studied in males, leaving a large gap in our understanding of these systems. Therefore, this project investigates signaling from the medial prefrontal cortex (mPFC) to the posterior hypothalamus (PH), a region that modulates stress responding and cardiovascular function, in both males and females. The function and anatomy of this circuit was tested with patch clamp electrophysiology and tracing studies in male and female Sprague Dawley and Long Evans rats (PND 72-141). Postsynaptic cell-type specificity was achieved using a transgenic GAD-Cre rat and Cre-dependent Colorschwitch virus and circuit-specific inputs were investigated with channelrhodopsin (ChR2). Anatomical tracing studies were both anterograde and retrograde to gain a comprehensive understanding of circuit organization and stress reactivity. Functionally, both action potential firing rates and spontaneous synaptic inputs support *in vivo* evidence that the PH is under tonic inhibitory control. The majority of PH neurons receive input from the mPFC, with no difference in the proportion of connected neurons between sex or postsynaptic cell type. Retrograde tracing elucidated significantly greater PH projection density in females compared to males within the tenia tecta (TT) and infralimbic (IL) regions of the ventral mPFC, with an equal proportion of PH-projecting mPFC neurons activated by acute restraint stress. Anterograde tracing revealed, surprisingly, that the density of IL terminals within the PH is comparable between male and female rats. Although females have a larger number of PH-projecting neurons within the IL, male and female PH have similar density of synaptobrevin-expressing IL presynaptic terminals. Together, these results indicate that males and females have similar synaptic connectivity between the IL and PH at the level of PH, but there is an anatomical distinction at the level of the mPFC. Data from this project help to elucidate the sexual divergence in the function of cortical-hypothalamic signaling and how cognitive and emotional signaling from the prefrontal cortex differentially regulates homeostasis and motivation between sexes.

Disclosures: C.A. Bouchet: None. E.C. Pinsinski: None. J.C. Cook: None. F.R. Stockley: None. C.E. Vaaga: None. B. Myers: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.10/R13

Topic: G.03. Stress and the Brain

Support: NIH RO1 HL150559

Title: Stress-activated visceral cortical projections to the ventrolateral medulla

Authors: *K. E. AYALA¹, S. A. PACE², D. E. MOORE¹, E. LUKINIC¹, F. R. STOCKLEY¹, B. MYERS¹;

¹Colorado State Univ., Fort Collins, CO; ²Salk Inst. for Biol. Studies, San Diego, CA

Abstract: Acute stress initiates physiological and psychological responses that are adaptive for organismal survival. However, chronic exposure to stress disrupts homeostasis, contributing to adverse effects on behavior and physiology. Consequently, chronic stress is a major risk factor for a multitude of health concerns, including heart disease, high blood pressure, and psychiatric disorders. Stress-related health consequences frequently exhibit sex-specific expression. However, the functional organization of brain wide circuitry underlying sex-specific physiological stress responses remains to be determined. The ventrolateral medulla (VLM) is a brain region integral for stress regulation. Within the VLM, the rostral VLM (RVLM) modulates sympathetic outflow, while the caudal VLM (CVLM) regulates the hypothalamic-pituitary-adrenal axis. Both regions are also key regulators of the baroreflex. The current study aims to characterize how stress-activated inputs to the RVLM and CVLM are organized in the brains of male and female rats. Retrograde-transported adeno-associated viruses expressing either green fluorescent protein (GFP) or mCherry were injected into the RVLM and CVLM. Test subjects underwent restraint stress prior to tissue collection, and c-Fos immunohistochemistry identified stress activation in RVLM-projecting and CVLM-projecting neurons. The focus was on the visceral cortical regions since these regions provide higher order input to the stress response. In particular, we examined the infralimbic cortex (IL), a brain area critical for cognitive appraisal of stress, and the insular cortex (IC), a central hub for processing interoceptive signals and emotional regulation. Results indicate widespread and largely segregated inputs to the RVLM and CVLM with varying degrees of stress reactivity from the IL and IC. The insular cortex contains a greater number of projecting neurons to the VLM with low stress-activation, whereas the infralimbic cortex had fewer projections with a majority of those projections being stress-activated. These findings present a framework for identifying integral brain regions involved in the sex-specific neural regulation of autonomic and neuroendocrine homeostasis.

Disclosures: K.E. Ayala: None. S.A. Pace: None. D.E. Moore: None. E. Lukinic: None. F.R. Stockley: None. B. Myers: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.11/R14

Topic: I.04. Executive Functions

Support: <https://doi.org/10.69777/352385>

Title: Transcriptional and Synaptic Dysregulation of mPFC-VTA Connectivity Underlies Cognitive Deficits Induced by Chronic Stress

Authors: *L. PANCOTTI¹, K. HUOT², S. MANSOURI², M. D'ANGELO⁴, C. PROULX³, B. LABONTÉ⁵;

¹Ctr. de recherche CERVO Univ. Laval, Québec, QC, Canada; ²Univ. Laval, Quebec, QC, Canada; ³Psychiatry and Neurosciences, Univ. Laval, Quebec City, QC, Canada; ⁴CERVO Brain Res. Ctr., Quebec, QC, Canada; ⁵Neurosci. and Psychiatry, Laval Univ., Quebec, QC, Canada

Abstract: Cortical dysregulation of subcortical circuits is increasingly recognized as a key mechanism underlying mood and cognitive disorders. The medial prefrontal cortex (mPFC) sends dense projections to the ventral tegmental area (VTA), a dopaminergic hub involved in motivation, reinforcement, and cognitive control. Chronic stress has been shown to induce structural and functional changes in mPFC neurons projecting to the VTA. However, the precise recruitment of this circuit during motivated behavior—and the synaptic and behavioral consequences of stress on its function—remain poorly understood. To investigate the circuit's engagement during cognitive processes, we performed pathway-specific calcium imaging using fiber photometry. We selectively expressed jRGECO in mPFC neurons projecting to the VTA and recorded the population activity *in vivo* during a working memory task. We observed time-locked calcium transients preceding decision points, indicating solid recruitment of this pathway during decision making. To explore the synaptic basis of this dysfunction, we combined optogenetics with ex vivo slice recordings. Optical stimulation of mPFC terminals in the VTA revealed a short-term potentiation of excitatory transmission onto dopaminergic neurons, which was markedly impaired in stressed animals. This facilitation was shown to depend on presynaptic calcium-interacting proteins, linking behavioral circuit recruitment with dynamic synaptic plasticity mechanisms. Underlying molecular mechanisms were investigated using RNA-seq on PFC neurons projecting to the VTA, revealing key targets involved in Ca²⁺ regulation at mPFC-VTA synapses. In females, the *Calhm1* gene, encoding a Ca²⁺ homeostatic protein, was significantly downregulated after stress. Using a CRISPR-based interference complex, we suppressed *Calhm1* expression in naïve females, mimicking stress-induced plasticity alterations at mPFC-VTA synapses. Finally, we evaluated cognitive performances in *Calhm1* KD mice and found impairments in working memory and cognitive assessment tasks, phenocopying chronic stress effects on cognitive performances. Overall, our findings highlight a novel form of plasticity at mPFC-VTA synapses underlying cognitive deficits induced by chronic stress. Therapeutic options targeting this pathway could improve stress-related cognitive deficits.

Disclosures: L. Pancotti: None. K. Huot: None. S. mansouri: None. M. D'Angelo: None. C. Proulx: None. B. Labonté: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.12/R15

Topic: G.03. Stress and the Brain

Support: NIH grant R21MH133108

Title: Inhibition of Glutamate but not GABA producing neurons in the Rostral Posterior Hypothalamus during repeated audiogenic stress attenuates habituation

Authors: *G. MISSBACH¹, L. ATKINSON³, C. NATH³, A. MORELLE³, S. CAMPEAU⁴, A. FLAKE^{3,2};

¹Psychology and Neurosci., ²Univ. of Colorado - Boulder, Boulder, CO; ³Univ. of Colorado-Boulder, Boulder, CO; ⁴Dept Psychol & Neurosci, and Ctr. for Neurosci., Univ. Colorado Boulder, Boulder, CO

Abstract: Chronic stress is associated with poor health outcomes including psychiatric illnesses and sensitization to stressors. However, repeated exposure to mild homotypic stressors results in stress habituation, defined as a reduced response to repeated stressors. Impaired ability to habituate to stressors is associated with mood disorders, likely due to increases in severity and length of stress responding to non-threatening stimuli. Previous work identified the rostral region of the Posterior Hypothalamus (rPH) as necessary for stress habituation to repeated audiogenic stress via muscimol inhibition of this region. The rPH is connected to multiple sensory regions and provides prominent inputs to stress effector systems like the raphe pallidus, paraventricular nucleus of the hypothalamus, and periaqueductal gray, that are responsible for autonomic, hormonal and behavioral responses, respectively. The current study uses selective inhibition of Glutamatergic and GABAergic neurons in the rPH during repeated stress exposure to assess the necessity of these cell populations for stress habituation. Male and female rats underwent 7 days of repeated audiogenic stress with DREADD based inhibition of Glutamatergic or GABAergic neurons in the rPH and were subsequently tested for stress responding with audiogenic stress with no DREADD inhibition. Both male and female rats showed significant habituation of stressor-induced heart rate and body temperature increases over 7 days. Inhibition of GABAergic neurons in the rPH during repeated audiogenic stress did not alter acute stress response or stress habituation. Inhibition of Glutamatergic neurons in the rPH during repeated audiogenic stress reduced acute stress response, and importantly impaired habituation. This finding strongly suggests that glutamatergic neuron activity, but not GABAergic activity in the rPH during repeated stress exposures is critical for proper stress habituation.

Disclosures: G. Missbach: None. L. Atkinson: None. C. Nath: None. A. Morelle: None. S. Campeau: None. A. Flake: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.13/R16

Topic: G.03. Stress and the Brain

Title: Reduced motor response to d-Amphetamine in Uromodulin knockout mice

Authors: *M. JONES^{1,2}, T. MEYER^{4,1}, K. D. FISCHER^{3,1}, K. LAFAVERS^{2,1};
²Anatomy, Cell Biol. and Physiol., ³Pharmacol. & Toxicology, ¹Indiana Univ. Sch. of Med., Indianapolis, IN; ⁴Stark Neurosciences Res. Inst., Indianapolis, IN

Abstract: Uromodulin (also known as Tamm-Horsfall Protein, THP) is a protein produced by the kidneys and released into both urine and blood, where its circulating form counteracts oxidative stress in the kidney, bloodstream, and other organs. We hypothesized that THP may play a protective role in the Central Nervous System (CNS), given that its antioxidant effects are mediated by the ion channel TRPM2, which is highly expressed in dopaminergic (DA) neurons. This is of particular interest given that damage to the kidney can result in transient or permanent neurological damage, though the mechanisms for this are not completely known. Previous studies have detected THP-positive cells in the rat CNS and in human cerebrospinal fluid, indicating THP's presence in the CNS, though its relationship to neuronal populations remains poorly understood. Because DA neurons are essential for motor control, we aimed to examine how THP influences motor function, both under baseline conditions and when DA activity is stimulated. To test this, we worked with the IU Behavioral Phenotyping Core and completed locomotor activity assessments on twelve male and female mice per genotype (THP^{+/+}, THP^{+/-} and THP^{-/-}), followed by measurement of food, water and fructose consumption and motor activity of each animal in a metabolic cage. Mice then received escalating doses of d-Amphetamine (d-AMP, up to 10 mg/kg) to activate DA signaling, with movement time and distance measured after each dose. Following phenotyping, we collected the brain, spinal cords, kidneys, and serum. THP^{-/-} mice showed no significant differences in number and duration of running bouts, stereotypy, and total movement time when compared to THP^{+/+} or THP^{+/-} controls. Metabolic cage measurements confirmed that THP^{-/-} mice consumed more water than controls and revealed a variable preference for fructose among THP^{-/-} mice. Following administration of d-AMP at 3 mg/kg, THP^{-/-} mice showed reduced distance travelled over time, with a stronger effect observed in females. This blunted response to d-AMP was also present in fructose-naïve mice, suggesting it was not attributable to prior testing stress. Because d-AMP enhances DA signaling in the brain, a reduction in movement after d-AMP administration implies that systemic THP may support midbrain DA neuronal function. This aligns with previous findings showing that THP can cross the blood-brain barrier (BBB) and that TRPM2 is expressed in DA neurons. Future work will focus on characterizing THP's interactions with DA neurons in both healthy and injury contexts, as well as elucidating the mechanisms by which THP crosses the BBB.

Disclosures: M. Jones: None. T. Meyer: None. K.D. Fischer: None. K. LaFavers: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.14/S1

Topic: G.03. Stress and the Brain

Support: Medical Research Council Grant
NIH Oxford-Cambridge Scholarship

Title: Cortical layer 6 Drd1a-Cre⁺ neurons serve as a neuromodulatory hub of cortical arousal by balancing dopaminergic, serotonergic, and orexinergic activation of the murine medial prefrontal cortex

Authors: *M. ABUELEM^{1,2,3}, L. MESSORE², F. CHEDOTAL^{2,4}, R. KYNE², D. A. LEOPOLD³, Z. MOLNÁR², E. O. MANN²;

¹Natl. Inst. of Hlth. / Univ. of Oxford, Bethesda, MD; ²Univ. of Oxford, Oxford, United Kingdom; ³NIH, Bethesda, MD; ⁴AgroParisTech, Univ. Paris-Saclay, Palaiseau, France

Abstract: Cortical layer 6 (L6) neurons play an important role in driving cortical arousal via the higher-order corticothalamic system. Many of these L6 neurons are remnants of the transient developmental subplate, which contains some of the earliest generated cortical neurons involved in the establishment of thalamocortical circuits and implicated in neurodevelopmental disorders like autism and schizophrenia. In the murine somatosensory and medial prefrontal cortex (mPFC), a subpopulation of L6 neurons expressing the dopamine D1 receptor (L6-*Drd1a*) selectively project to higher-order thalamic nuclei and are highly sensitive to the wake-promoting neuropeptide orexin, playing an important role in gating cortical arousal and anxiety behavior. Serotonergic psychedelics like psilocin have also shown promising effects in reducing anxiety-like behavior. However, the modulatory mechanisms through which L6-*Drd1a* neurons mediate dopaminergic and serotonergic-driven mPFC activation in relation to orexin remain poorly understood. Thus, we investigated the effects of chronic genetic ‘silencing’ of L6-*Drd1a* neurons using a *Snap25* conditional knockout mouse model (*Drd1a-Cre*^{+/+}; *Snap25*^{fl/fl}; *tdTomato*^{STOPfl/fl}) on the dopaminergic, serotonergic, and orexinergic modulation of network activity in mPFC acute slices using high-density multielectrode arrays and whole-cell patch clamp recordings. We found that D1 receptor (D1R) agonist SKF-81297 and 5-HT2A receptor (5-HT2AR) agonist psilocin selectively increased L6-*Drd1a* intrinsic excitability and local network activity in the ventral and dorsal mPFC, respectively, which was eliminated upon ‘silencing’ L6-*Drd1a* neurons. On the other hand, D2 receptor (D2R) agonist quinpirole non-selectively excited L6 neurons and only increased ventral mPFC network activity in L6-*Drd1a* ‘silenced’ slices. These results demonstrate that D1R and 5-HT2AR activation (along with previously reported orexin 2 receptor (OX2R) activation) increase L6-*Drd1a* excitability to drive mPFC network arousal along a dorsal-ventral gradient. They also suggest a compensatory mechanism of D2R activation in the functional absence of L6-*Drd1a* neurons. Interestingly, simultaneous application of psilocin and OX2R agonist YNT-185 eliminated the mPFC network activation in control slices by each agonist alone. This suggests a balancing mechanism between 5-HT2AR-expressing and OX2R-expressing L6 neurons in regulating mPFC network activity. Our findings provide novel insight into the role of mPFC L6-*Drd1a* neurons as a

neuromodulatory hub of cortical arousal, with therapeutic implications for anxiety and stress-related disorders.

Disclosures: M. Abuelem: None. L. Messore: None. F. Chedotal: None. R. kyne: None. D.A. Leopold: None. Z. Molnár: None. E.O. Mann: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.15/S2

Topic: I.04. Executive Functions

Support: JSPS 21H04858
JSPS 23K17448
JSPS 24H00670
JSPS 23KJ0248
JST JPMJMI19D5
JST JPMJSP2124

Title: Enhancement of Prefrontal Executive Function Mediated by Cardiac Vagal Activity Following Low-Dose Hypoxic Gas Inhalation: A fNIRS study

Authors: *D. LEE¹, Y. YAMAZAKI², R. KUWAMIZU^{2,3}, M. OKAMOTO^{2,3}, H. SOYA^{2,4};
¹Inst. of Hlth. and Sport Sciences, Univ. of Tsukuba, Tsukuba-shi, Ibaraki, Japan; ²Inst. of Hlth. and Sport Sci., ³Advanced Res. Initiative for Human High Performance (ARIHHP), ⁴Ctr. for Cybernics Res., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Modern life imposes a range of psychophysiological stressors, such as strict time constraints and fast-paced lifestyles, which can lead to dysfunction in cardiac parasympathetic activity. This disruption is closely linked to increased risks of mental health problems and declines in essential executive functions. While physical exercise enhances cardiac vagal activity (CVA) and cognition, it is not feasible for everyone, particularly those with physical or psychological limitations. This highlights the need for accessible exercise mimetics that can promote CVA and support executive function. Our recent study (J Physiol Sci, 2025) showed that 10 minutes of inhaling low-dose hypoxic gas (FIO₂: 13.5%) acts as a hormetic stressor. Specifically, it induces a transient decrease in oxygen saturation, accompanied by an increased heart rate and reduced CVA, which subsequently triggers a compensatory rebound characterized by enhanced CVA and a reduction in heart rate below baseline levels. Notably, no symptoms of acute mountain sickness or related adverse effects were observed, supporting the safety of this intervention. CVA mediates brain-heart communication, particularly *via* the left dorsolateral prefrontal cortex (L-DLPFC), which is central to executive function. Based on this, we hypothesized that acute hypoxic gas inhalation would enhance executive function by enhancing CVA. Twenty-six individuals participated in both normobaric hypoxia (NH, FIO₂: 13.5%) and

normoxia (NN, ambient air) conditions in a within-subjects design. CVA was assessed *via* heart rate variability, with the root mean square of successive differences (RMSSD). HRV was recorded at three time points: before, during, and after each inhalation session. Executive function was evaluated using the Stroop task before and after inhalation, and prefrontal cortical activity during the task was monitored using multichannel functional near-infrared spectroscopy, focusing on the L-DLPFC. Following hypoxic gas inhalation, RMSSD showed a supercompensation along with a concurrent reduction in heart rate. In the NH condition, Stroop task performance improved, accompanied by greater task-related activation in the L-DLPFC. Causal mediation analysis indicated that the post-hypoxia increases in RMSSD mediated both the improvement in Stroop performance and the increase in L-DLPFC activation. These findings support our hypothesis that enhancement of CVA following hormetic hypoxic stress contributes to improved executive function, implicating exercise-mimetic effects and broadening neurocognitive strategies for enhancing executive performance.

Disclosures: D. Lee: None. Y. Yamazaki: None. R. Kuwamizu: None. M. Okamoto: None. H. Soya: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.16/S3

Topic: G.03. Stress and the Brain

Support: Foundation for Economic Education for the PoDoCo grant:5-880-28

Title: Acute effects of endurance exercise on brain activity - a meg study with physiological and affective markers

Authors: *S. KUMPULAINEN^{1,2}, J. PELTONEN², E. HAAPALA³;

¹Active Life Lab., South-Eastern Finland Univ. of Applied Sci., Mikkeli, Finland; ²Polar Electro Oy, Kempele, Finland; ³Fac. of Sport and Hlth. Sci., Univ. of Jyväskylä, Jyväskylä, Finland

Abstract: Exercise is a well-established non-pharmacological intervention for improving mental health, yet the neural processes through which it exerts these benefits remain poorly understood. To optimize its use, a deeper understanding of the brain mechanisms underlying its effects is needed. We investigated acute changes in alpha power dynamics following a 30-minute cycling exercise at self-selected intensity, aligned with principles self-efficacy theory. Twenty-one participants underwent magnetoencephalography (MEG) recordings before, 10 min and 45 min after exercise. Affective well-being was assessed via questionnaire before each MEG measurement, and heart rate (HR) was continuously monitored. On average, participants cycled at 75% of their maximal HR (SD = 8), with lower-fit individuals tending to select lighter and higher-fit individuals heavier intensities. Results showed immediate ($p < .05$) and sustained increases ($p < .01$) in alpha power across the frontal, parietal, and occipital areas, with training-

specific changes limited to the left occipital area. The FOOOF analysis confirmed that exercise affected the brain's rhythmic activity. Increases in alpha power immediately after exercise were correlated with better aerobic fitness ($r(19) = .63, p = .002$) and higher exercise intensity ($r(19) = .51, p = .018$), while later changes were significantly linked only to higher respiratory rate ($r(18) = .59, p = .006$). This suggests that while immediate brain responses may be blunted in individuals with lower fitness, benefits can still emerge over time. Negative affect decreased immediately ($p < .001$) and continued to decline ($p = .018$), while positive affect increased only after 45 minutes ($p = .010$). A trend-level correlation between increased positive affect and alpha power at 45 minutes post-exercise was also observed ($p = .41, p = .064$). Higher exercise intensity elicited stronger alpha modulation and greater affective improvements than lower intensities. Altogether, these findings advance our understanding of the brain-body mechanisms underlying the emotional benefits of exercise and emphasize the underrecognized role of the occipital cortex—a novel finding likely enabled by MEG's high spatial resolution. The occipital cortex is increasingly recognized as a multisensory hub involved in integrating internal and external bodily signals. Our finding of breathing-related alpha power increases may reflect a transition from external sensory engagement toward a more internally focused state. The results underscore the potential of intensity-appropriate exercise for mood regulation, with implications for its integration into mental health care.

Disclosures: S. Kumpulainen: None. J. Peltonen: None. E. Haapala: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.17/S4

Topic: G.03. Stress and the Brain

Title: Three-minute breathing space meditation reduces stress-related EEG frontal alpha asymmetry and mood symptoms in postgraduate students: protocol for a randomized controlled trial

Authors: *Z. LIU;

Universiti Putra Malaysia, Fac. of Med. and Hlth. Sci., serdang, Malaysia

Abstract: Postgraduate students experience high levels of stress, with substantially elevated rates of anxiety and depression compared to the general population. However, busy schedules and time constraints often hinder their engagement in stress-reduction practices. Brief mindfulness meditation has emerged as a promising intervention to reduce stress with minimal time investment. This ongoing randomized controlled trial examines the efficacy of an ultra-brief mindfulness practice, the 3-minute Breathing Space meditation, in reducing stress among postgraduate students. A total of 156 master's and PhD students (stratified by nationality) will be recruited and randomized in a 1:1 ratio to either the Breathing Space Meditation group or a waitlist control group. Participants in the intervention arm will practice guided 3-minute

breathing meditation four times per week for 8 weeks (32 sessions total), integrated into their daily routines. Assessments will be conducted at baseline and post-intervention (8 weeks). The primary outcome is self-reported stress levels, measured by the Depression Anxiety Stress Scales-21 (DASS-21) stress subscale. Secondary outcomes include anxiety and depression (DASS-21 subscales), physiological stress markers (salivary cortisol and C-reactive protein), and a neurophysiological measure (EEG frontal alpha asymmetry). General self-efficacy (GSE) will also be measured to explore its role as a mediator of psychological outcomes. Planned analyses include mixed-effects linear models to assess intervention effects over time, dynamic network analysis to examine the temporal interplay among stress, anxiety, and depression symptoms, and mediation analysis to test whether changes in GSE mediate the intervention's effects on outcomes. As data collection has not yet commenced, results are not available at this time. This study will provide a comprehensive multi-level evaluation of a brief meditation intervention. By integrating psychological, endocrine, and neurophysiological measures, it will yield insights into the multifaceted effects of brief mindfulness practice and inform accessible stress reduction strategies for high-stress student populations.

Disclosures: Z. Liu: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.18/S5

Topic: I.04. Executive Functions

Support: Australian Spinal Research Foundation

Title: Effects of chiropractic adjustments on prefrontal cortex activity and acute stress using functional near-infrared spectroscopy (fNIRS): A pilot randomized controlled trial.

Authors: *N. KUMARI¹, I. AMJAD¹, I. NIAZI¹, U. GHANI¹, Y. ZIANG², N. JIANG², H. HAAVIK¹;

¹Ctr. for Chiropractic Res., New Zealand Col. of Chiropractic, Auckland, New Zealand; ²Sichuan Univ., Chengdu, China

Abstract: Chiropractic adjustments are proposed to modulate central and autonomic nervous system function, yet their effects on prefrontal cortex (PFC) responses to acute stress are not well understood. This pilot randomized controlled trial investigated whether a single chiropractic session alters PFC activity and subjective stress during acute stress exposure, using functional near-infrared spectroscopy (fNIRS). Twenty-four adults with subclinical spinal pain (mean age 30 ± 8.6 years; 16 males) were randomized to chiropractic or control interventions. PFC activity was measured with fNIRS (NIRSIT, OBELAB) at rest, during stress task preparation, during the Maastricht Acute Stress Test (MAST), and at rest after MAST, both before and after intervention. MAST combined physical (cold pressor) and psychological (mental arithmetic

under evaluative threat) stressors. Subjective stress was assessed using an 11-point numeric rating scale (SNRS-11). Both groups demonstrated significant increases in subjective stress during MAST. However, following intervention, the chiropractic group exhibited a significantly attenuated stress response compared to controls (MAST 5-min: 4.33 ± 0.58 vs. 5.08 ± 1.21 , $p < 0.05$; linear mixed model adjusting for baseline). The chiropractic group also maintained lower stress scores at 10-min post-MAST. fNIRS analysis revealed increased activation in dorsolateral and orbitofrontal PFC regions in the control group after the acute stress challenge, while the chiropractic group showed stable or reduced PFC activation post-intervention, consistent with enhanced neural efficiency and resilience. In the control group, subjective stress correlated strongly with prefrontal activation ($r = 0.76$, $p < 0.01$), whereas this relationship was absent in the chiropractic group, indicating a decoupling of perceived stress and neural response after intervention. These findings suggest chiropractic care may confer neuroprotective effects during acute stress challenge, supporting improved stress regulation via prefrontal network integration and autonomic modulation.

Disclosures: N. Kumari: None. I. Amjad: None. I. Niazi: None. U. Ghani: None. Y. Ziang: None. N. Jiang: None. H. Haavik: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.19/S6

Topic: G.03. Stress and the Brain

Support: VA Grant #I01BX005923

Title: Investigating the use of CORT response to a mild stressor as a predictor of traumatic stress susceptibility

Authors: *E. A. DEVINE¹, J. B. CHAMBERS², B. A. PACKARD⁴, J. P. HERMAN³;
¹Univ. of Cincinnati, Cincinnati, OH; ²Pharmacol. & Systems Physiol., Univ. of Cincinnati, Independence, KY; ³Dept Pharmacol. and Systems Physiol., Univ. of Cincinnati, Cincinnati, OH; ⁴Neurosci, Univ. Cincinnati, Cincinnati, OH

Abstract: The mammalian stress response is a critical function for survival. Upon threat detection, the hypothalamo-pituitary-adrenocortical (HPA) axis is activated, unleashing a neuroendocrine signaling cascade culminating in secretion of glucocorticoids (GC). GCs facilitate the redistribution of energy to enhance survival and restore homeostasis. Exposure to traumatic stress can cause GC signaling dysfunction and may contribute to stress-related diseases such as post-traumatic stress disorder (PTSD). PTSD alters the brain's emotional processing by promoting a hyper-aroused state expressed as anxiety, hypervigilance, avoidance, impulsivity, and memory deficits. While many individuals experience trauma, only a portion go on to develop PTSD. Acquiring deeper insight into the variables contributing to PTSD susceptibility is crucial

for improved identification and treatment of at-risk individuals. Human studies have found correlations between pre- and post-stress cortisol levels and PTSD development and symptom severity, while rodent studies indicate similar findings between corticosterone (CORT) and PTSD-like behavioral deficits. Given this information, our study aimed to determine whether CORT response to a mild stressor can predict behavioral outcomes after later exposure to single-prolonged stress (SPS), a rodent model of traumatic stress (second hit). Male and female rats were exposed to a light-dark box, and plasma CORT was collected across 4 time points post-exposure. Area under the curve (AUC) of the LD response was used to separate rats into high and low CORT responder groups. These responder groups were then either assigned as controls or exposed to SPS. Starting 1 week post-SPS, rats completed a battery of fear and anxiety-related behavioral testing, including elevated plus maze, open field, novel object recognition, social interaction, and cued fear conditioning. In males, CORT response to mild stress had no effect on post-SPS behavioral outcomes for any of the 5 tests run. However, SPS-exposed female high CORT responders froze more during extinction and reinstatement than their control high CORT responder counterparts, as well as both control and SPS-exposed low CORT responders. AUC was positively correlated with freezing behaviors during fear conditioning among SPS-exposed females, while no such correlation existed among controls. These data suggest that high CORT responsiveness to mild stress could predict individuals who are susceptible to behavioral deficits post-SPS exposure among females.

Disclosures: E.A. Devine: None. J.B. Chambers: None. B.A. Packard: None. J.P. Herman: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.20/S7

Topic: G.03. Stress and the Brain

Support: NIH MH096889
NIH NS108286
NIH MH132680

Title: Characterization of novel CRH projection cells in the basolateral amygdala

Authors: *Y. CHEN^{1,2}, M. T. BIRNIE², T. BARAM³;

¹Univ. of California-Irvine, Tustin, CA; ²Dept. of Pediatrics, ³Anatomy/Neurobiology; Pediatrics, Univ. of California-Irvine, Irvine, CA

Abstract: Background: The basolateral amygdala (BLA) is a heterogeneous nuclear complex and projects to brain regions involving in reward, fear, and stress responses. Projections connecting brain regions are typically composed of several cell types defined by their neurotransmitter and often by a co-expressed neuropeptide. We have reported a GABAergic projection from the BLA

to the nucleus of accumbens (NAc) that expresses neuropeptide corticotropin-releasing hormone (CRH) (Birnie *et al.*, *Nat Commun* 2023), while the majority of the literature suggests that the BLA-NAc projection is glutamatergic. Specifically, this BLA-NAc GABAergic CRH+ projection represses reward behavior. Neuropeptide CRH has well-established roles in stress, addiction, and reward via specific cellular actions within NAc and several other brain regions, providing impetus for the comprehensive characterization of BLA-CRH projection cells. Here, we characterize CRH-expressing cells in the BLA and map BLA-CRH projections in mouse brain. Methods: The cellular identity of BLA-CRH cells and their projection targets within mouse brain were investigated by employing transgenic mice, anterograde and retrograde viral-genetic tracing, coupled with *in situ* hybridization, 3D imaging, and multiple immunostainings. Results: CRH cells in the BLA exclusively co-localized with GAD mRNA and protein, but not glutamatergic markers. Optogenetic stimulation of the BLA-CRH projections in the NAc yielded IPSCs. Anterograde tracing via injection of pAAV-FLEX-tdTomato into the BLA of *Crh-IRES-Cre* mice identified CRH expressing projections from the BLA to the NAc, bed nucleus of the stria terminalis (BNST), prefrontal cortex (PFC), and ventral hippocampus (vHip). The delivery of retro-AAVs into above projection targets ascertained distinct subgroups of CRH projection cells in the BLA with apparent neuroanatomical segregation within the BLA. Combined retrograde tracing and multiple immunostainings suggested that BLA-CRH projection cells can be classified into different subgroups, and some of them send collateral projections. Conclusions: GABAergic CRH expressing cells across the BLA are projection cells, targeting brain regions important for stress, reward, and cognition. These cells can be classified as distinct subgroups and each subset of cells sends axonal projection, contacting with its specific target cells.

Disclosures: Y. Chen: None. M.T. Birnie: None. T. Baram: None.

Poster

PSTR031: Stress-Modulated Pathways

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR031.21/S8

Topic: G.03. Stress and the Brain

Title: Effects on intestinal motility and acute stress with different euthanasia methods in rats

Authors: *M. ENRIQUEZ-BETANCOURT¹, D. E. CASTILLO-ROLON²;

¹Facultad de Medicina Veterinaria y Zootecnia, UNAM, Mexico City, Mexico; ²Fisiología-Facultad de Medicina Veterinaria y Zootecnia UNAM, Fac. of Vet. Med. and Zootechnics, Ciudad de Mexico, Mexico

Abstract: For research purposes, different methods of euthanasia are carried out on animals for further experimentation and study of various phenomena in-vivo and in-vitro. One of the most employed methods of euthanasia in research is CO₂ inhalation. However, in recent years, the collateral effects in terms of physiological and emotional stress in animals have been studied. The combination of anesthesia followed by CO₂ inhalation is an alternative euthanasia method to

the exclusive use of CO₂. In the study of the contractile activity of intestinal smooth muscle, different techniques can be used. In vitro techniques are spread used in research and teaching for pharmacology, toxicology, or for the study of physiological components related to the autonomic nervous system and the enteric nervous system. The present study compares the effects of 3 different euthanasia methods and acute stress on intestinal smooth muscle motility. The experimental groups are 3-month-old female Wistar rats (n=24; 12 males and 12 females) divided into 4 groups: euthanasia with CO₂ (30%); anesthesia with sodium pentobarbital (70 mg/kg) followed by CO₂ inhalation (30%); anesthesia with tiletamine-zolazepam (7mg/kg) followed by CO₂ inhalation (30%); pentobarbital overdose 3 times the maximum dose (70 mg/kg). Measurements include recording the strength and frequency of intestinal smooth muscle contractions in vitro, through the BIOPAC data acquisition unit and BSL PRO software; and measurement of acute stress blood biomarkers (ACTH). In the case of intestinal tissue, the changes observed may be due to a modification in intestinal motility, related to the euthanasia method itself or indirectly, in response to the acute stress presented by the animal after the euthanasia method used. We evaluate these changes through measurements in the strength and frequency of smooth muscle in the wall of the gastrointestinal tract and observed variations among the experimental groups. Through taking a basal register, group 2 (pentobarbital + CO₂) results indicate more strength and frequency of contractions, comparatively from others, while group 1 (CO₂) has the lowest strength and frequency in contractions; ACTH concentrations (pg/dl) were lower in group 2, comparatively with group 1. Differences between males and females were also observed.

Disclosures: M. Enriquez-Betancourt: None. D.E. Castillo-Rolon: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.01/S9

Topic: G.06. Autonomic Regulation

Support: NIH Grant U41NS129436

Title: Vaginal blood flow responses to sacral neurostimulation in a sheep model

Authors: *S. A. BHASKARAN, A. C. LAGUNAS, M. S. NISSEN, M. ORTIZ-LOPEZ, T. M. BRUNS;

Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Female sexual dysfunction (FSD) affects approximately 40% of adult women in the United States and can be detrimental to quality of life and interpersonal relationships. Despite its prevalence, FSD remains poorly understood and there are few effective treatments. Electrical stimulation of nerve targets, including the sacral nerve, tibial nerve, and dorsal genital nerve, has been shown to alleviate symptoms of FSD, potentially related to increases in vaginal perfusion.

However, optimization of neurostimulation treatments for FSD is difficult due in part to the large parameter space and the lack of physiologically relevant animal models for conducting in-depth parameter exploration. The goal of this study is to characterize vaginal blood flow responses to stimulation of the sacral nerve at different amplitudes and frequencies in an in vivo sheep model. A vaginal photoplethysmography (VPP) sensor is used to measure vaginal perfusion of the sheep under anesthesia. A series of trials are performed in which VPP is measured at baseline followed by stimulation of either 30 seconds or 5 minutes in length with a cuff electrode implanted on a sacral nerve. This is repeated at varying stimulation amplitudes (between 0.5 and 10 times motor threshold) and frequencies within 1 to 33 Hz. Analysis is performed on changes in the peak-to-peak amplitude of the VPP signal between baseline and stimulation periods. Preliminary data from two animals indicate that the sheep vagina can easily accommodate a human vaginal photoplethysmography sensor. Sheep VPP signals display a similar sawtooth shape and amplitude to VPP signals measured in humans, suggesting that the sheep is a suitable model for vaginal perfusion. Consistent increases (~20%) in the VPP signal were observed as a result of 30 seconds of stimulation at 33 Hz and amplitudes between 1.2 and 6.7 times the motor threshold. Less consistent increases in VPP were also observed during 5 minutes of stimulation at 14, 20, and 33 Hz. This work explores the first use of sheep as a model for developing a neuromodulation treatment for FSD and will inform the development of a more optimal treatment protocol for use in humans.

Disclosures: S.A. Bhaskaran: None. A.C. Lagunas: None. M.S. Nissen: None. M. Ortiz-Lopez: None. T.M. Bruns: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.02/S10

Topic: G.06. Autonomic Regulation

Support: NIH Grant U41NS129436

Title: Quantifying sacral evoked compound action potential variations during controlled bladder filling in a large animal model

Authors: *M. S. NISSEN¹, A. C. LAGUNAS², S. A. BHASKARAN¹, M. ORTIZ-LOPEZ², T. M. BRUNS²;

²Biomed. Engin., ¹Univ. of Michigan, Ann Arbor, MI

Abstract: Sacral neuromodulation (SNM) is an FDA approved treatment for a variety of lower urinary tract and pelvic dysfunctions. SNM involves applying low-amplitude electrical current to the sacral nerve trunk, usually the S3. The underlying mechanisms that contribute to SNM's therapeutic efficacy are not well understood. Recently, advances in neuromodulation have seen increased use of evoked compound action potentials (ECAPs) in clinical settings. ECAPs have

been useful as feedback for closed-loop control paradigms in spinal cord stimulation for pain. Sacral evoked compound potentials (SECAPs) have been shown to exist in humans during SNM. While it has been shown that these potentials may change under different postures, it is not clear if physiological states may alter SECAPs. In this study, we use bladder filling as a method of altering the afferent activity of the sacral nerve. Bladder fullness is of interest as if there is a change in SECAPs during bladder filling, then there might be potential to use SECAPs as a feedback mechanism for modifying SNM parameters in closed-loop stimulation. Here we use sheep as an animal model, which is a good SNM model due to their size being more proportional to humans than other popular animal models. In sheep, we implanted a stimulating electrode proximal on the S2 or S3 sacral nerve and a multi-contact recording cuff electrode at least 2 cm distal to the stimulating electrode. We can use the spatial differences between contacts on the recording cuff to estimate what part of the nerve is being activated. We then filled the bladder at 30 mL per minute with and without SNM (14 Hz or 33 Hz) until a bladder pressure of 30 cmH₂O was reached. SECAPs increased in magnitude with increasing applied current. SECAPs being of neural origin was confirmed by applying lidocaine distal to the recording cuff and then proximal to the recording cuff. There was a marked reduction in SECAP magnitude following application of lidocaine proximal to the recording cuff. We were able to observe different SECAP magnitudes when selectively stimulating around the nerve. We will examine SECAP's potential as a source of feedback for closed-loop SNM, by determining if SECAPs change under different bladder filling stages.

Disclosures: M.S. Nissen: None. A.C. Lagunas: None. S.A. Bhaskaran: None. M. Ortiz-Lopez: None. T.M. Bruns: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.03/S11

Topic: G.06. Autonomic Regulation

Title: Effects of electroacupuncture and guided meditation on autonomic regulation, gastrointestinal function, and attention in patients with spleen qi deficiency syndrome

Authors: *S. QUIROZ-GONZÁLEZ¹, I. JIMENEZ-ESTRADA², J. RAMÍREZ GÓMEZ³;
¹Univ. Estatal del Valle de Ecatepec., Ecatepec, Mexico; ²Physiology, Biophysics and Neurosci., IPN Ctr. Invst & Adv Studies, Mexico City, Mexico; ³State Univ. of Ecatepec Valley, Ecatepec, Mexico

Abstract: In Traditional Chinese Medicine (TCM), Spleen Qi Deficiency Syndrome (SQDS) is associated with gastrointestinal, immune, and cognitive disturbances. This study assessed the effects of electroacupuncture (EA) plus meditation on heart rate variability (HRV), gastrointestinal symptoms, intestinal peristalsis, and attentional performance in SQDS patients recruited from the Integrated University Clinic. Participants were randomly assigned to five

groups: control (n=39), SQDS (n=67), sham EA (n=34), EA (n=52), and EA+meditation (n=58). The EA treatment used 1.5 cun stainless steel needles with a 4 mm diameter, applied to the following acupoints: ST-25 (Tianshu), ST-36 (Zusanli), SP-6 (Sanyinjiao), SP-15 (Daheng), PC-6 (Neiguan), LI-11 (Quchi) bilaterally, and CV-6 (Qihai), CV-12 (Zhongwan) 2/15Hz. In the EA+meditation group, participants received a 30-minute guided visualization meditation focused on digestive system, performed concurrently with the EA. HRV was assessed via electrocardiography (ECG; MP150 Biopac Digital System, USA), analyzing beat-to-beat fluctuations (SDNN), high- and low-frequency components (HF, LF), and the LF/HF ratio. Peristalsis was evaluated using surface electrogastrography (EGG, MP150 Biopac Digital System, USA). Attention was evaluated using the d2 Test. Patients with SQDS exhibited significantly lower total HRV (SDNN) compared to controls ($p<0.05$). EA increased HRV, and the combination of EA and meditation produced a greater improvement. HF components were reduced in SQDS patients ($p<0.023$), while LF and the LF/HF ratio were elevated. These parameters were significantly improved in both the EA group ($p<0.05$) and the combined EA+meditation group ($p<0.01$). Regarding gastrointestinal symptoms, patients with SQDS scored higher on the total scale, abdominal pain, indigestion, and constipation dimensions compared to controls ($p<0.05$), and improved after EA, with larger reductions in the EA+meditation group. In the d2 attention test, the SQDS group made more errors ($26.4\%\pm 2.1$; $p=0.017$), had a higher error rate ($19.6\%\pm 11.1$; $p=0.014$), and showed greater performance fluctuation ($17\%\pm 2.7$; $p=0.02$). Concentration performance was lower compared to controls ($15\%\pm 1.9$; $p=0.024$). After EA treatment, patients showed reduced total errors, error rate, and fluctuation (21.43%, 15.11%, and 14.38%, respectively), along with improved concentration scores. Combined EA+meditation yielded greater cognitive improvements than EA alone. Results suggest that EA plus meditation modulate the autonomic balance by enhancing parasympathetic tone, improving attention and gastrointestinal function in SQDS patients.

Disclosures: S. Quiroz-González: None. I. Jimenez-Estrada: None. J. Ramírez Gómez: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.04/S12

Topic: G.06. Autonomic Regulation

Title: The insular cortex regulates autonomic nervous activity, heart rates, intestinal motility, and blood glucose levels

Authors: *R. SHIRATORI¹, T. YOKOI², K. KINOSHITA², W. XUE², N. KUGA^{2,3}, T. SASAKI^{2,4};

¹Dept. of Pharmacology, Fac. of Pharmaceut. Sci., Tohoku Univ., Miyagi, Japan; ²Dept. of Pharmacology, Fac. of Pharmaceut. Sci., Tohoku Univ., Miyagi, Japan; ³Creative

Interdisciplinary Res. Division, Frontier Res. Inst. for Interdisciplinary Sciences, Tohoku Univ., Miyagi, Japan; ⁴Dept Neuropharmacol, Grad Sch. Med, Tohoku Univ., Miyagi, Japan

Abstract: The brain maintains bodily homeostasis by sending signals to peripheral organs, such as heart, intestine and pancreas, via the autonomic nervous systems to adjust bodily states. The insular cortex plays a central role in bodily homeostasis and is suggested to receive peripheral signals reflecting the current state of peripheral organs and regulate peripheral organ activity to minimize the discrepancy between the current state and the homeostatic set point. However, how the insular cortical activity controls the physiological activities of each peripheral organs remain fully unclear. To elucidate the contribution of the insular cortex to the regulation of the heart, intestine, and pancreas, we recorded electrocardiogram signals, intestinal myoelectrical signals and blood glucose levels in freely moving rats while inactivating insular cortex through infusion of a GABA_A receptor agonist muscimol. Inhibition of the insular cortical activity significantly reduced heart rates and intestinal motility, and increased variability of blood glucose levels. These peripheral signals are suggested to be controlled through the autonomic nervous system. To evaluate the effect on autonomic nervous system activity, including sympathetic or parasympathetic nerves, power spectral analysis of heart rate variability on the electrocardiogram was performed. We found that the insular cortical inhibition decreases the low-frequency components of the heart rate variability spectrum, reflective of sympathetic activity, and also decreases the high-frequency components, reflective of parasympathetic control. These results suggest that the insular cortex regulates peripheral physiological signals such as heart rate, intestinal motility, and blood glucose levels through the modulation of both sympathetic and parasympathetic tone.

Disclosures: R. Shiratori: None. T. Yokoi: None. K. Kinoshita: None. W. Xue: None. N. Kuga: None. T. Sasaki: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.05/T1

Topic: G.06. Autonomic Regulation

Support: NIH T32AG049688
AHA 18PRE33960254
ADA #1-17-ACE-31
NIH R01DK124461
DOD W81XWH-20-1-0345

Title: Amygdala-liver signaling orchestrates rapid glycemic responses to stress and drives stress-induced metabolic dysfunction

Authors: *J. R. E. CARTY¹, K. DEVARAKONDA², R. M. O'CONNOR³, P. J. KENNY⁴, S. STANLEY⁵;

¹Icahn Sch. of Med. at Mount Sinai, New York, NY; ²Sci. writer/editor, New York, NY;

³Neurosci., Mount Sinai Sch. of Med., New York, NY; ⁴Neurosci., Icahn Sch. of Med. At Mount Sinai, Tarrytown, NY; ⁵Diabetes, Obesity and Metabolism Inst., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: When an animal encounters a threat in the environment or other stressful stimuli, it must rapidly mobilize energy stores to support appropriate defensive behaviors, such as escape, darting, or freezing. Rapid energy mobilization fuels cardiovascular and muscular responses to stress and supports the increased allocation of cognitive resources necessary to process threat-relevant contextual information. In parallel, behavioral repertoires that could compete with defensive strategies, such as foraging and eating, must be suppressed. Glycemic responses to stress are correlated with fight-flight behaviors, and glucose infusions elicit stress-like enhancements of cardiac output and blood pressure, in addition to facilitating the encoding of spatial memories. These threat-induced metabolic adaptations are highly conserved across species, suggesting they provide a strong evolutionary advantage. Despite their biological importance, surprisingly little is known about the brain circuits that orchestrate adaptive hyperglycemic and hypophagic responses to acute stress.

In this study, we show that acute stress activates medial amygdala (MeA) neurons that innervate the ventromedial hypothalamus (MeA^{VMH} neurons), which precipitates hyperglycemia and hypophagia. The glycemic actions of MeA^{VMH} neurons occur independently of adrenal or pancreatic glucoregulatory hormones. Instead, using whole-body virus tracing, we identify a polysynaptic connection from MeA to the liver, which promotes the rapid synthesis of glucose by hepatic gluconeogenesis. We demonstrate that recurrent stress disrupts amygdalar-liver circuit activity to drive stress-related metabolic abnormalities, thereby linking chronic stress to metabolic disorders such as type 2 diabetes (T2D). Our findings reveal a novel amygdala-liver axis that regulates rapid glycemic adaptations to stress and links recurrent stress to metabolic dysfunction.

Disclosures: J.R.E. Carty: None. K. Devarakonda: None. R.M. O'Connor: None. P.J. Kenny: None. S. Stanley: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.06/T2

Topic: G.06. Autonomic Regulation

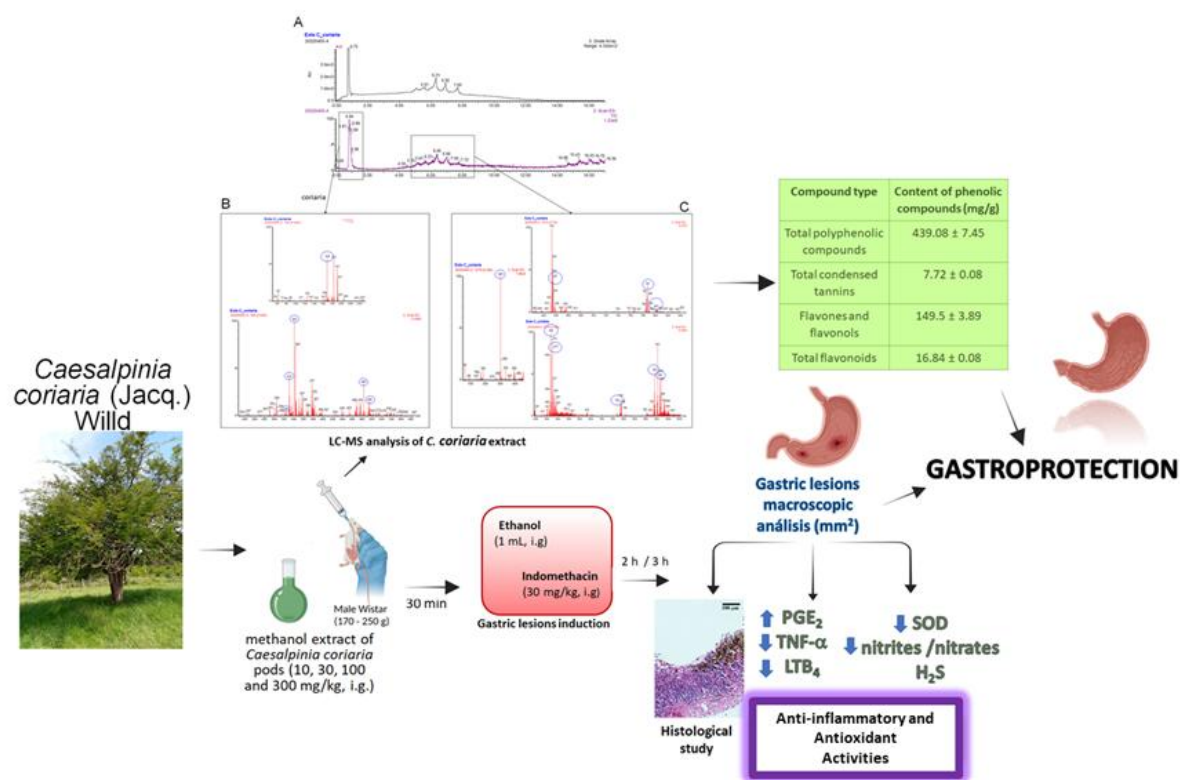
Support: Programa de Apoyo a Proyectos de Investigaci3n e Innovaci3n Tecnol3gica (PAPIIT), Direcci3n General de Asuntos del Personal Acad3mico (DGAPA), Universidad Nacional Aut3noma de M3xico [grant number IA200721]

Title: Gastroprotective effect of methanol extract of *Caesalpinia coriaria* pods against gastric damage in a murine model

Authors: *E. A. PINEDA¹, A. REYES RAMÍREZ², A. CHAVEZ PIÑA⁴, A. NAVARRETE-CASTRO³;

¹Facultad de Estudios Superiores Zaragoza, Univ. Nacional Autónoma De México (UNAM), México, Mexico; ²Facultad de Estudios Superiores Zaragoza, Univ. Nacional Autónoma De México (UNAM), Ciudad de México, Mexico; ³Facultad de Química, Univ. Nacional Autónoma De México (UNAM), Mexico City, Mexico; ⁴Escuela Nacional de Medicina y Homeopatía, Inst. Politécnico Nacional, Ciudad de México, Mexico

Abstract: Gastric damage is a prevalent worldwide disease with multiple etiologies including inflammatory activity and reactive oxygen species generation. The therapies available for the management of gastric damage are associated with side effects that limit their use. *Caesalpinia coriaria* (Jacq.) Wild is used as a traditional medicinal plant in Mexico for the treatment of gastrointestinal diseases. Therefore, our research aims is to investigate the gastroprotective effect of extract of *Caesalpinia coriaria* pods against ethanol-induced and indomethacin-induced gastric lesion models, its anti-inflammatory and antioxidative activities, and its main compounds through LC-MS analysis. Methods. male Wistar rats were orally administered a methanol extract obtained from the pods of *C. coriaria* (at doses of 10, 30, 100, and 300 mg/kg) prior to inducing gastric lesions with ethanol or indomethacin. Gastric mucosal lesions were evaluated by macroscopic and histopathological alterations. Determination of prostaglandin E₂ (PGE₂), alpha necrosis factor (TNF- α), leukotriene B₄ (LTB₄), nitrites/nitrates, superoxide dismutase (SOD) and H₂S gastric levels were investigated. Results and Conclusion. Phenolic compounds were identified as major component of methanol extract, the significant compounds were gallic acid, 3-O galloylquinic acid, and ellagic acid. Pretreatment with the extract at doses of 100 and 300 mg/kg significantly reduced gastric ulcer lesions in both models. The extract's gastroprotective effect was accompanied by significant decreases in leukocyte recruitment, and gastric levels of TNF- α and LTB₄ by two to fourfold ($p < 0.05$). Also, gastric levels of PGE₂ were maintained and the antioxidant enzyme activity of SOD and nitrate/nitrite in the gastric tissue were improved ($p < 0.05$). The results suggest that the gastroprotective effect of the methanol extract of *C. coriaria* pods occurs through anti-inflammatory, antioxidant, and NO modulation properties, and gallic acid derivatives may be the main possible compounds responsible for its actions.



Disclosures: E.A. Pineda: None. A. Reyes Ramírez: None. A. Chavez Piña: None. A. Navarrete-Castro: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.07/T3

Topic: G.06. Autonomic Regulation

Support: Craig H. Neilsen
DoD CDMRP TRA

Title: Exploring effective treatment window for intradetrusor botulinum toxin in a rodent model of spinal cord injury

Authors: *L. N. CATES¹, M. HUDSON¹, Z. Z. KHAING²;

¹Univ. of Washington, Seattle, WA; ²Neurolog. Surgery, Univ. of Washington, Louisville, KY

Abstract: Despite modern bladder management methods, lower and upper urinary tract complications still contribute significantly to morbidity and diminished quality of life in persons with spinal cord injuries (SCIs). Neurogenic overactive bladders (OAB) often develop after SCI,

and this can result in loss of compliance and concomitant urinary tract complications. Currently, there is no treatment available to prevent the development of neurogenic bladder for patients with SCI. However, intradetrusor injections of botulinum toxin A (BoNT-A) are approved and often performed at the chronic state of OAB to chemodenervate and relax bladder muscles. We theorize that the prolonged state of overactivity of the bladder after SCI which precedes the BoNT-A intervention results in muscle, nerve, and tissue damage that can be prevented by acute and/or early chemodenervation. Here we present the results of bladder functional studies in which rats sustained contusion type spinal cord injury at T7/8 or a sham injury (n=3) and either received saline (n=7) or intradetrusor BoNT-A injections immediately (acute, n=8), 3 days post injury (dpi, n=7), 1 week post injury (wpi, n=7), or 2wpi (n=5) and we performed cystometry studies at 6 - 8 wpi for all animals. We found that acute BoNT-A treatment after SCI resulted in improved bladder capacity and compliance, increased regularity of voiding contractions, and shortened intermicturition intervals compared to 3dpi, 1wpi, 2wpi, or saline treated SCI animals. In fact, the delay of BoNT-A treatment resulted in a corresponding reduction in bladder function preservation in bladder compliance, capacity, and intermicturition intervals. While not all data reached statistical significance we are greatly encouraged by the pattern in our findings; the longer the delay in chemodenervating the overactive bladder appears to result in poorer preservation of normal bladder function. Additionally, significant decreases in CGRP-positive sensory fibers in the dorsal horn and GAP-43 expression were seen in acute BoNT-A treated SCI animals compared to SCI animals with no bladder treatment. Acute treatment with BoNT-A shows promising results in stabilizing normal bladder function after a spinal cord injury. Future studies exploring the effective length of time and potential for redosing could help establish a more translatable treatment protocol for SCI and OAB patients.

Disclosures: L.N. Cates: None. M. Hudson: None. Z.Z. Khaing: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.08/T4

Topic: G.06. Autonomic Regulation

Support: SNSF P500PB_206880
NIH-NIDDK DK125708

Title: Defining the molecular and spatial organization of spinal circuits regulating lower urinary tract function

Authors: *A. M. SARTORI^{1,2}, N. KLYMKO², A. M. VERSTEGEN^{1,2};
¹Harvard Med. Sch., Boston, MA; ²Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Lower urinary tract function (LUTF) relies on the seamless coordination of autonomic and somatic pathways to control urine storage and voiding. Several brain regions have been

implicated in regulating LUTF; however, the spinal cord is the critical hub for integrating sensory inputs and generating motor outputs essential to bladder control. Yet, the specific spinal neurons that mediate these functions remain largely undefined. Previous efforts have outlined the general locations of neurons regulating LUTF within the spinal cord, but their cellular identities and molecular characteristics have remained unclear. To address this gap, we leveraged a cFos-based TRAP2::H2B-Trap transgenic mouse model to permanently tag neurons activated during repeated bladder infusion in awake animals, thereby enabling selective enrichment of LUTF-relevant neurons from the lumbosacral spinal cord (L6-S2). We performed single-nuclei RNA sequencing on both TRAP-enriched and non-enriched samples, generating a comprehensive transcriptional atlas of over 20,000 neurons. Clustering analysis identified approximately 30 molecularly distinct subpopulations, including excitatory and inhibitory interneurons with either local or long-range projections, as well as autonomic and somatic motor neurons. To complement the molecular profiling with spatial resolution, we applied high-resolution spatial transcriptomics using the 10X Visium HD platform on cross-sections of the lumbosacral spinal cord. Using the snRNA-seq dataset as a reference, we mapped transcriptionally defined neuronal populations to anatomically distinct regions implicated in lower urinary tract control, including the intermediolateral cell column, dorsal gray commissure, and superficial lateral dorsal horn. In parallel, the enhanced resolution of Visium HD enabled comprehensive characterization of non-neuronal cell types, providing an integrated view of the cellular environment within LUTF-relevant spinal regions. Ongoing studies are examining the connectivity and functional roles of these regionally distinct clusters. In addition, we are applying single-nuclei RNA-sequencing to the human sacral spinal cord with the goal of identifying conserved neuronal populations across species. Together, this work provides an unprecedented molecular and spatial map of LUTF-related spinal circuits, deepens our understanding of the spinal regulation of this visceral function, and establishes a foundation for translating these findings into human systems and future therapeutic strategies.

Disclosures: A.M. Sartori: None. N. Klymko: None. A.M. Verstegen: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.09/T5

Topic: G.06. Autonomic Regulation

Support: NIH IRACDA Grant K12GM081266-17
NIH Grant R21AG086774-01

Title: A novel estrogen-sensitive hypothalamus-brainstem neurocircuit for voluntary control of micturition

Authors: *L. E. CABRERA-ZAPATA¹, W. C. KRAUSE¹, Y. J. ZHENG¹, A. VENKATARAMAN¹, K. K. STIETZ², X. DUAN³, H. A. INGRAHAM¹;

¹Dept. of Cell. and Mol. Pharmacology, Sch. of Medicine, Univ. of California San Francisco, San Francisco, CA; ²Dept. of Comparative Biosciences, Sch. of Vet. Medicine, Univ. of Wisconsin, Madison, WI; ³Dept. of Ophthalmology, Sch. of Medicine, Univ. of California San Francisco, San Francisco, CA

Abstract: The ventrolateral ventromedial hypothalamic nucleus (VMHvl) coordinates reproductive behavior and metabolism through an intricate, close crosstalk with other hypothalamic nuclei. However, less is known about its influence on neuronal populations outside the hypothalamus, such as the brainstem. With this in mind, we first mapped the VMHvl neuronal projections into the brainstem specifically for the estrogen receptor alpha (ER α)/melanocortin receptor 4 (MC4R)-expressing neurons regulating physical activity and energy expenditure. Stereotaxic injection of a Cre-dependent anterograde trans-synaptic tracer into the VMHvl of *Mc4r-t2a-cre* mice revealed Barrington's nucleus (Bar), a central regulator of micturition, as one of the main target regions for the VMHvl^{MC4R} synaptic input in the pons. We then used chemogenetics to specifically interrogate the role of VMHvl^{MC4R} neurons in micturition. Remarkably, chemogenetic activation of the VMHvl^{MC4R} node completely blocked micturition for at least 2 h during Void Spot Assay (VSA), even when mice were pre-loaded with a maximum dose of saline (20 ml/kg, i.p.). This physiologic response correlated with increased cFOS expression in Vgat-positive GABAergic neurons in Bar. Notably, similar results were found in 22-month-old aged female mice. Chemogenetic inhibition of VMHvl^{MC4R} neurons showed opposite effects. We further confirmed the inhibitory effect of VMHvl^{MC4R} activity on micturition by uroflowmetry and cystometry, the latter clearly revealing a strong suppression of bladder contraction and voiding following VMHvl^{MC4R} chemogenetic stimulation. Finally, activation of VMHvl^{MC4R} neurons also blocked colonic motility, with an average 4-fold reduction in the number of fecal events detected during uroflowmetry (4 h) and a major delay in colonic transit time. Altogether, our data place the VMHvl^{MC4R} node as a novel, inhibitory modulator of Bar activity in the micturition pathway, with potential relevance for therapeutic use in alleviating urinary incontinence.

Disclosures: L.E. Cabrera-Zapata: None. W.C. Krause: None. Y.J. Zheng: None. A. Venkataraman: None. K.K. Stietz: None. X. Duan: None. H.A. Ingraham: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.10/T6

Topic: G.06. Autonomic Regulation

Title: Rem sleep suppression during diazoxide induced acute hyperglycemia in a non diabetic mouse model

Authors: *P. BANIYA, C. CHEONG, E. YOON, T. KIM;
Dept. of Biomed. Sci. and Engin., Gwangju Inst. of Sci. and Technol., Gwangju, Korea,
Republic of

Abstract: Sleep is fundamental to metabolic homeostasis. Disruptions of sleep and circadian rhythms lead to impaired glucose regulation and hormonal signaling, which in turn promote the development of metabolic syndrome. In diabetes mellitus, sleep disturbances are prevalent and often attributed to secondary complications such as nocturia; however, the frequent concurrence of hyperglycemia and sleep impairment suggests a complex, bidirectional relationship. Despite emerging evidence linking metabolic state and sleep physiology, the mechanisms by which acute hyperglycemia directly modulates sleep architecture remain poorly elucidated. In this study, we established an acute hyperglycemic mouse model by administering glucose solution via oral gavage and diazoxide intraperitoneally to mice that had been fasted for 8 hours. Diazoxide, a potassium channel opener used clinically to treat insulinoma and congenital hyperinsulinism, induces hyperglycemia by inhibiting insulin secretion from pancreatic β -cells through activation of ATP-sensitive potassium channels. Diazoxide induces hyperglycemia by inhibiting insulin secretion from pancreatic β -cells via activation of ATP-sensitive potassium channels. Fasting blood glucose concentrations equal to or exceeding 200 mg/dL were used as a threshold to define hyperglycemia. These mice exhibit transient hyperglycemia, lasting approximately six hours, which provides a suitable model for investigating sleep-wake dynamics. Diazoxide was dissolved in DMSO, used as the vehicle control, while saline served as the negative control. This six-hour hyperglycemic period sleep recording reveals a suppression of REM sleep, characterized by a reduced percentage of REM sleep, shorter REM bout length, and decreased average REM duration. The findings also suggest that acute hyperglycemia significantly reduces absolute power across all vigilance states, with the most pronounced decreases observed during wakefulness and non-rapid eye movement (NREM) sleep. This indicates a substantial dampening of cortical activity under hyperglycemic conditions. These findings provide new insights into the direct impact of acute glucose dysregulation on sleep regulation, advancing our understanding of the physiological interplay between metabolic state and sleep architecture.

Disclosures: P. Baniya: None. C. cheong: None. E. Yoon: None. T. Kim: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.11/T7

Topic: G.06. Autonomic Regulation

Support: NIH Common Fund (Award 3OT2OD030541)

Title: Sckan: Exploring autonomic nervous system connectivity through a curated knowledge base with ai-enhanced query capabilities

Authors: ***I. ZIOGAS**¹, F. T. IMAM², T. GILLESPIE², S. TAPPAN³, J. BOLINE⁴, M. C. SURLES-ZEIGLER², J. S. GRETHE², B. DE BONO⁵, M. E. MARTONE²;

¹SPARC K-Core, La Jolla, CA, United States, San Diego, CA; ²Dept. of Neurosciences, Univ. of California San Diego, La Jolla, CA; ³Rock Maple Sci., Hinesburg, VT; ⁴Informed Minds Inc, Walnut Creek, CA; ⁵Whitby et al., LLC, Indianapolis, IN

Abstract: The NIH SPARC Connectivity Knowledge Base (SCKAN) addresses critical gaps in understanding peripheral nervous system connectivity by integrating and curating detailed knowledge of peripheral and autonomic nervous system connectivity across species, anatomical regions, and phenotypes. Built on FAIR data principles, SCKAN represents connectivity statements in a structured, machine-readable format with rich metadata including neuron population soma and axon locations, phenotypes (e.g., sensory, sympathetic, parasympathetic), species, sex, and laterality. SCKAN draws from expert curation, SPARC datasets, and a natural language processing pipeline processing millions of biomedical publications. In 2025, new tools were introduced to make SCKAN's rich content more accessible. These include SCKANNER, a heatmap-based visualization of population frequencies; SPARC MAPS, an interactive anatomical context map of connectivity; and SCKAN NLI, an LLM-powered natural language interface trained solely on curated SCKAN data, providing hallucination-free, verifiable answers. This suite empowers researchers to seamlessly visualize and query SCKAN's contents, while the newly developed SCKAN Composer tool facilitates efficient curation and modeling of connectivity knowledge. Use cases demonstrate how SCKAN supports exploration of sex-specific pathways (e.g., reproductive systems innervations), species-specific pathways (e.g., comparison of human, mouse, and pig connectivity), and laterality differences (e.g., asymmetric pathways in cardiac, kidney, or reproductive systems). SCKAN's population-based modeling framework enables systematic identification and visualization of knowledge gaps in sex-specific, species-comparative, and laterality research. This approach transforms peripheral connectivity research by providing structured access to phenotypically-specified neural populations, supporting precision neuromodulation approaches that account for biological diversity in autonomic connectivity patterns. SCKAN and its tools are available in the SPARC Portal.

Disclosures: **I. Ziogas:** None. **F.T. Imam:** None. **T. Gillespie:** None. **S. Tappan:** None. **J. Boline:** None. **M.C. Surles-Zeigler:** None. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc.. **B. de Bono:** None. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch Inc..

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.12/T8

Topic: G.06. Autonomic Regulation

Support: Cold Spring Harbor Laboratory and Northwell Health Affiliation

Title: Gfral neurons mediate intestinal type 2 immunity

Authors: *D. VAN DE LISDONK^{1,2}, O. ESKIOCAK¹, B. LI¹;

¹Cold Spring Harbor Lab., Cold Spring Harbor, NY; ²SILS center for neuroscience, Amsterdam, Netherlands

Abstract: Increasing evidence highlights the importance of the central nervous system (CNS) in regulating allergic responses, also in the context of food allergies. While food allergies were once considered relatively uncommon, their prevalence has risen significantly in recent years among both children and adults. Recent studies have identified a critical function for growth differentiation factor 15 (GDF15) released in the intestine and acting on the brain, particularly in mediating avoidance behavior associated with food allergies. However, the exact neural circuits and mechanisms by which GDF15 contributes to the modulation of immune responses in the context of food allergy remain poorly understood. In this study, we focus on a specific population of neurons located in the area postrema (AP) and the nucleus of the solitary tract (NTS), these neurons uniquely express GDNF family receptor α -like (GFRAL), which to date is the only known receptor for GDF15. We demonstrate by using a food allergy model in mice, GFRAL-expressing neurons exhibit significantly increased activity, suggesting their involvement in the central processing of allergic signals. Interestingly, enhanced neuronal activation of GFRAL neurons is sufficient to induce a type 2 immune response in the intestine. Additionally, we observe that chronic activation of this neuronal population leads to impaired nutrient absorption resulting in body weight loss. Together, our findings suggest the existence of a positive feedback loop in which food allergy stimulates GFRAL-expressing neurons in the brainstem, and the activation of these neurons further mediates the intestinal type 2 immune response. This neuro-immune pathway may represent a novel mechanism by which the brain contributes to type 2 immunity and represents a promising target for therapeutic intervention targeting neuro-immune communication.

Disclosures: D. van de Lisdonk: None. O. Eskiocak: None. B. Li: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.13/T9

Topic: G.06. Autonomic Regulation

Support: NIH Grant R01 DK128475
NIH Grant R01 DK140445
NIH Grant R01 DK139386
Takeda Science Foundation Fellowship Program

Title: In vivo simultaneous electromyogram recordings from pelvic organs

Authors: *M. KAWATANI¹, H. GREENHILL², F. LIU³, Y. ZHANG³, M. HEITMEIER¹, L. YANG⁴, H. HAHM³, V. K. SAMINENI⁵;

²Anesthesiol., ¹Washington Univ. in St. Louis, St. Louis, MO; ³Washington Univ. in St. Louis, St. Louis, MO; ⁴Anesthesiol., Washington Univ. in St. Louis Neurosci. PhD Program, St. Louis, MO; ⁵Washington Univ., St. Louis, MO

Abstract: Mammalian excretory processes—such as voiding and defecation—are precisely coordinated by the activity of multiple pelvic organs. Disruption of this coordination can lead to a profound loss in quality of life. Electromyogram (EMG) recordings in animal models are often used for functional evaluation, however, limited to anesthetized settings due to technical obstacles. Here, we report the use of a recently developed soft, implantable EMG array (Myomatrix, Chung et al., 2023) to record simultaneously from multiple pelvic targets in vivo. Each flexible electrode shank was implanted into one of the following tissues: detrusor muscle (bladder), colonic smooth muscle, external urethral sphincter and external oblique muscle. We successfully obtained stable EMG signals from each of these organs in freely moving mice. These recordings demonstrate (1) baseline activity patterns across all implanted sites and (2) the organ-specific EMG responses to physiological stimuli such as bladder filling. Our results illustrate that a multi-site, flexible EMG array can capture coordinated muscle activity across the pelvic complex, even in small, conscious animals. This approach opens new avenues for studying pelvic-organ cross-talk under normal and pathological conditions and may ultimately facilitate the development of therapies for urinary and bowel disorders.

Disclosures: M. Kawatani: None. H. Greenhill: None. F. Liu: None. Y. zhang: None. M. Heitmeier: None. L. Yang: None. H. Hahm: None. V.K. Samineni: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.14/T10

Topic: G.06. Autonomic Regulation

Title: Neurotrophins beyond the nervous system in fish: distribution, expression and potential functions

Authors: *A. CARRILLO MUÑOZ¹, F. CASTELÁN², S. Y. RODRIGUEZ JAIMES³, G. HERNÁNDEZ HERNÁNDEZ¹;

¹Univ. Autónoma de Tlaxcala, Tlaxcala, Mexico; ²Inst. de Investigaciones Biomedicas, UNAM, Tlaxcala, Mexico; ³Univ. Autónoma De Tlaxcala, Tlaxcala, Mexico

Abstract: Introduction

Trophic factors like neurotrophins (NGF, BDNF, NT-3, NT4/5, NT6/7) are essential for key cellular processes including differentiation, growth, survival, and regeneration. Their high morphological and phylogenetic conservation across animals suggests conserved biological

functions. **Context in Fish**

Fish, the oldest and most diverse group of vertebrates, show neurotrophin activity not only in the central nervous system but also across many peripheral tissues: Systems involved: mechanosensory, muscular, skin, respiratory, circulatory, digestive, endocrine, urinary, reproductive, and immune. This broad distribution suggests roles in development and maintenance of multiple organs and systems.

Key Findings

Although studies beyond the nervous system have focused on only 12 fish species, they show: BDNF and NT-3: Highly expressed in mechanosensory and digestive tissues. NGF: Predominantly expressed in mechanosensory and urinary systems. Expression and localization patterns are tissue-specific, highlighting specialized roles.

Conclusions & Future Directions

Further research is needed to explore the specific functions and mechanisms of neurotrophins across diverse fish species and tissues. This could deepen our understanding of organ development, regeneration, and maintenance, with potential implications for both comparative biology and regenerative medicine.

Disclosures: A. Carrillo Muñoz: None. F. Castelán: None. S.Y. Rodriguez Jaimes: None. G. Hernández Hernández: None.

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.15/T11

Topic: G.06. Autonomic Regulation

Support: NIH Common Fund Award OT2 OD03054
NIH Grant U24NS135547
NIH Common Fund Award 3OT3OD025349

Title: Increasing the value of data to the PNS research community through SPARC

Authors: *S. TAPPAN¹, J. BOLINE², F. T. IMAM³, I. ZIOGAS⁶, J. S. GRETHE⁷, T. GILLESPIE⁴, J. B. BOCCANFUSO⁸, D. P. NICKERSON¹⁰, T. J. PRICE¹¹, S. ZANOS¹², Z. CHENG¹³, J. B. WAGENAAR⁹, P. HUNTER¹⁴, M. E. MARTONE⁵;
¹Rock Maple Sci., Hinesburg, VT; ²Informed Minds Inc, Walnut Creek, CA; ³UCSD, SAN DIEGO, CA; ⁴Neurosci., UCSD, San Diego, CA; ⁵Neurosci., UCSD, La Jolla, CA; ⁶SPARC K-Core, La Jolla, CA, United States, Milan, Italy; ⁷Neurosciences, Ctr. for Res. in Biol. Systems, Neurosciences, Univ. of California San Diego, La Jolla, CA; ⁸Informatics, ⁹Dept. of Biostatistics, Epidemiology and Informatics, Univ. of Pennsylvania, Philadelphia, PA; ¹⁰Auckland Bioengineering Inst., Univ. of Auckland, Auckland, New Zealand; ¹¹Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas Neurosci. Undergraduate Program, Richardson, TX; ¹²Bioelectronic Med., Feinstein Inst. For Med. Res., Roslyn Heights, NY; ¹³Burnett Sch. of

Biomed. Sci., Univ. of Central Florida, Orlando, FL; ¹⁴Auckland Bioengineering Institute, Univ. of Auckland, Auckland, New Zealand, Auckland, New Zealand

Abstract: Understanding the interplay between interoception, the autonomic nervous system (ANS), and pain is crucial for advancing chronic pain treatment. Dysregulation across these systems contributes to persistent pain, highlighting the need for a holistic, integrative research approach—one that bridges physiological and anatomical perspectives without being constrained by disciplinary silos.

The SPARC Portal (<https://sparc.science>) offers an open-access, comprehensive resource featuring datasets, models, analytical tools, devices, and expert insights. Initially designed to support SPARC-funded research on neuromodulatory control of cardiovascular, gastrointestinal, respiratory, and urinary functions, the Portal has expanded through contributions from Helping to End Addiction Long-Term (HEAL)-funded researchers. These additions include data on the molecular and cellular basis of pain and models of joint sensory innervation, transforming the Portal into a robust platform for hypothesis generation, pilot studies, and exploratory research. To fully realize the potential of this resource, promoting data reuse is essential. This involves not only demonstrating the scientific value of existing datasets through targeted use cases and success stories but also lowering barriers to access and engagement. The SPARC Portal supports these efforts with intuitive discovery tools, interactive visualizations, API access, and thorough documentation. Educational resources—such as tutorials, webinars, and example workflows—further enable researchers from a range of disciplines to make effective use of the data. Here we highlight how the SPARC ecosystem fosters discovery, accelerates knowledge generation, and supports data reuse. Through specific examples, we show how researchers can leverage these resources to conduct novel analyses, develop preliminary findings, and identify new targets for neuromodulation and pain management studies.

Disclosures: **S. Tappan:** None. **J. Boline:** None. **F.T. Imam:** None. **I. Ziogas:** None. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc.. **T. Gillespie:** None. **J.B. Boccanfuso:** None. **D.P. Nickerson:** None. **T.J. Price:** None. **S. Zanos:** None. **Z. Cheng:** None. **J.B. Wagenaar:** None. **P. Hunter:** None. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc..

Poster

PSTR032: Autonomic Regulation: Gastrointestinal, Renal, Urinary, and Reproductive

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR032.16/T12

Topic: G.06. Autonomic Regulation

Support: Grants-in-Aid for Scientific Research (KAKENHI) [Research Project Number: 23H00360]
Grant-in-Aid for JSPS Fellows [Research Project Number: 24KJ1212]

Title: Oxytocinergic neurons projecting from the hypothalamus to the medullary raphe nucleus cause stress-induced defecation in rats.

Authors: *N. YUKI¹, T. SAWAMURA², H. YAMAGUCHI³, T. SHIINA^{1,4}, Y. SHIMIZU^{1,4};
¹Lab. of Physiology, Joint Grad. Sch. of Vet. Sciences, Gifu Univ., Gifu-shi / Gifu-ken, Japan;
²Inst. for Glyco-core Res. (iGCORE), Gifu Univ., Gifu-shi / Gifu-ken, Japan; ³Div. of Multicellular Circuit Dynamics, Natl. Inst. for Physiological Sci., Okazaki-shi / Aichi-ken, Japan; ⁴Ctr. for One Med. Innovative Translational Res. (COMIT), Inst. for Advanced Study, Gifu Univ., Gifu-shi / Gifu-ken, Japan

Abstract: <Background&Aim> The mechanism by which acute stress elicits defecation reflex is not well understood. In rats, it has been reported that activation of descending serotonergic neurons projecting from the medullary raphe to the lumbosacral spinal cord cause stress-induced defecation. In this study, we focused on the neurons located upstream of the medullary raphe to identify the neural pathways involving stress-induced defecation.<Methods> Rats were injected with a retrograde tracer, FluoroGold (FG), into the medullary raphe and neurons projecting to the nucleus were labelled. To verify whether the FG-labelled brain regions regulate colorectal motility, we microinjected of (S)-AMPA, a glutamate agonist, to the regions in urethane-anesthetized rats. Then colorectal motility was assessed in vivo by measuring intraluminal pressure and expelled fluid volume from the anus. <Results> In the hypothalamus, FG-positive cells were observed in the paraventricular hypothalamic nucleus (PVH) and the dorsomedial hypothalamus (DMH). When (S)-AMPA was unilaterally administered to the PVH or the DMH, a marked increase in colorectal intraluminal pressure that was associated with increased expelled fluid was observed. The increased motility was suppressed by the prior administration of dolasetron and ketanserin, serotonin receptor antagonists, in the lumbosacral spinal cord. Additionally, the increased motility was suppressed by the prior administration of L-368,899, an oxytocin receptor antagonist, to the raphe. Specific inhibition of the hypothalamus→medullary raphe pathway by the DREADD (designer receptors exclusively activated by designer drugs) suppressed the increased colorectal motility due to AMPA injection. Similarly, defecation induced by water avoidance stress was suppressed by DREADD-based inhibition of these pathways in conscious rats.<Conclusions> Stress-responsive hypothalamic neurons projecting to the raphe nucleus activate descending serotonergic neurons via oxytocinergic signalling, thereby stimulating colorectal motility through the pelvic nerves. These pathways are suggested to be novel neural pathways inducing defecation under stressful conditions.

Disclosures: N. Yuki: None. T. Sawamura: None. H. Yamaguchi: None. T. Shiina: None. Y. Shimizu: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.01/T13

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH R35GM140854
NIH R01NS111220 (CDD)
NIH R01HL153916

Title: A Brain Reward Circuit Inhibited By Next-Generation Weight Loss Drugs

Authors: *T. GUNGUL¹, E. N. GODSCHALL², I. R. SAJONIA¹, O. D. LI¹, K. MALIK¹, A. D. GULER¹;

¹Biol., Univ. of Virginia, Charlottesville, VA; ²Biol., Univ. of Virginia, Charlottesville, VA

Abstract: The obesity epidemic has heightened interest in glucagon-like peptide-1 receptor agonists (GLP1RAs), such as liraglutide and semaglutide, for their effects on weight loss and appetite suppression. GLP1RAs influence both homeostatic and hedonic feeding behaviors, though their neural mechanisms are not fully understood. In this study, we identified a population of GLP1R-expressing neurons in the central amygdala (CeA) that increase activity in response to GLP1RAs and, when activated, significantly reduce food intake in mice. Anatomical tracing showed that CeA-GLP1R neurons project to the ventral tegmental area (VTA), linking them to mesolimbic dopamine modulation. Activation of CeA-GLP1R neurons attenuates dopamine output in the nucleus accumbens (NAc) in response to high-fat diet (HFD), highlighting the role of the CeA-VTA-NAc circuit in modulating reward.

Disclosures: T. Gungul: None. E.N. Godschall: None. I.R. Sajonia: None. O.D. Li: None. K. Malik: None. A.D. Guler: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.02/T14

Topic: G.08. Food and Water Intake and Energy Balance

Support: 5I01BX004102
5R01DK115976
P30DK017047

Title: The anti-obesity effect of tirzepatide is augmented by systemic oxytocin treatment in male diet-induced obese rats

Authors: *A. L. WILLIAMS¹, M. GOLDBERG¹, T. WOLDEN-HANSON¹, M. W. SCHWARTZ^{2,3}, J. E. BLEVINS^{1,2};

¹Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA; ²Dept. of Medicine, Div. of

Metabolism, Endocrinol. and Nutr., ³UW Med. Diabetes Inst., Univ. of Washington Sch. of Med., Seattle, WA

Abstract: Chronic administration of the neurohypophyseal hormone, oxytocin (OXT), reduces body weight (BW) in high fat diet (HFD)-induced obese (DIO) rodents and non-human primates (rhesus monkeys). One advantage of chronic OXT treatment is that reduced food intake and weight loss can be induced without adverse gastrointestinal (GI) side effects (nausea, vomiting, diarrhea). By comparison, the anti-obesity effects of the long-acting dual glucagon-like peptide 1-receptor (GLP-1R)/glucose-dependent insulintropic polypeptide receptor (GIPR) agonist, tirzepatide (TZP), are commonly associated with adverse GI effects. In the current work, we sought to determine whether weight loss induced by a low dose of TZP (below that associated with adverse GI effects) can be augmented by systemic OXT administration without inducing an aversive response. To optimize dosing, adult chow-fed rats received one of four TZP doses (1, 3, 6 and 10 nmol/kg, subcutaneous (SC)) or its vehicle (VEH; TBS, pH 8.0) in a cross-over design so that each animal was used as its own control. Food intake (chow), kaolin intake (surrogate measure of visceral illness) and BW were measured daily. As expected, TZP (3, 6 and 10 nmol/kg) reduced BW gain after a single acute injection (by -0.5 ± 1.3 , -1.4 ± 0.7 and -4.9 ± 3.3 grams, respectively; $P < 0.05$), effects that were associated with reduced food intake ($P < 0.05$). The higher dose of TZP (10 nmol/kg) was also associated with increased kaolin diet intake ($P < 0.05$), while lower doses (3 nmol/kg and 6 nmol/kg) were not ($P = \text{NS}$). To determine if OXT can be combined with a low dose of TZP to increase weight loss without causing adverse GI effects, we studied rats rendered obese by placing them on a HFD for 9 months. Each rat was then implanted SC with a 28-day minipump that infused either OXT (50 nmol/day) or VEH (saline), and subsequently received a daily SC injection of an escalating dose of either TZP (1, 3 and then 6 nmol/kg) or VEH. Food intake and BW were measured daily, and body composition assessed pre- and post-intervention. Relative to pre-infusion BW, treatment with OXT (50 nmol/day) or TZP alone (1, 3 and then 6 nmol/kg dosing regimen) reduced BW by approximately $6.8 \pm 1.6\%$ ($P < 0.05$) and $6.2 \pm 1.1\%$ ($P < 0.05$), respectively. When OXT (50 nmol/day) was combined with TZP (1, 3 and then 6 nmol/kg), the BW reduction was nearly doubled ($11.3 \pm 0.8\%$ $P < 0.05$) ($N = 5-7/\text{group}$). While this effect was associated with reductions of both food intake ($P < 0.05$) and body fat mass ($P = 0.051$), kaolin intake was not increased. We conclude that in a rat model of DIO, the anti-obesity efficacy of low-dose TZP can be amplified by OXT without eliciting detectable GI side effects.

Disclosures: A.L. Williams: None. M. Goldberg: None. T. Wolden-Hanson: None. M.W. Schwartz: None. J.E. Blevins: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.03/T15

Topic: G.08. Food and Water Intake and Energy Balance

Support: HKRGC_GRF 14112523
HKRGC_GRF 14113522
HKRGC_GRF 14122124

Title: The μ -opioid receptor in the BNST regulates food intake through synergistic presynaptic and postsynaptic modulation

Authors: *Y. ZHU¹, S. WANG², Y. KE¹;

¹The Chinese Univ. of Hong Kong, Hong Kong, China; ²City Univ. of Hong Kong, Hong Kong, China

Abstract: As a key component of the extended amygdala, the bed nucleus of the stria terminalis (BNST) integrates stress and reward signals and regulates diverse behaviors, including anxiety, addiction, and feeding. Although μ -opioid receptors (MORs) are abundantly expressed in the BNST, their functional roles remain elusive. Given the involvement of the opioid system in modulating appetite and hedonic feeding, we investigated how MOR activation influences BNST neural activity and feeding behavior. We found that bilateral microinjection of the MOR agonist DAMGO into the anterior BNST (aBNST) robustly promoted food intake in sated rats, with a preference for high-fat diet. To explore the underlying cellular effects, we conducted whole-cell patch-clamp recordings in brain slices. Drugs were delivered via micro-perfusion through a separate glass pipette to achieve focal activation of the patched neurons. We found that DAMGO induces strong inhibition of aBNST neurons through a postsynaptic mechanism. Notably, the degree of hyperpolarization varied across subregions of the aBNST. Moreover, DAMGO uniformly reduced spontaneous excitatory synaptic transmission across aBNST subregions but suppressed inhibitory inputs in a region-selective manner. These findings suggest that MOR activation in the aBNST modulates feeding behavior by orchestrating both somatic excitability and synaptic inputs in a subregion-specific manner. Our study reveals a novel mechanism by which BNST MOR signaling shapes appetite, offering new insights into the neural circuits underlying feeding and potential targets for treating disordered eating.

Disclosures: Y. Zhu: None. S. Wang: None. Y. Ke: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.04/T16

Topic: G.08. Food and Water Intake and Energy Balance

Support: COBRE Grant P20GM130461
Nebraska Tobacco Settlement Biochemical Research Funds (to K.T.W.)

Title: Melanin-concentrating hormone neuron activity increases in response to sensory stimuli and before free drinking of sugar and sugar-sweetened alcohol cocktails

Authors: *I. R. K. KUEBLER¹, J. CHIN², J. VOLLAN², M. SUAREZ², K. T. WAKABAYASHI²;

²Psychology, ¹Univ. of Nebraska-Lincoln, Lincoln, NE

Abstract: Sweet Flavored Alcoholic Beverages (FABs), also known as ready-to-drink cocktails, have risen in popularity in recent years. While FAB research often focuses on taste alone, glucose in some FABs can enter the brain and impact the activity of key neuronal systems. One of these brain systems, melanin-concentrating hormone (MCH), regulates both sugar and alcohol seeking and intake, but it is unknown how the activity of MCH neurons contributes to these behaviors. Recently we found that added glucose potentiates alcohol drinking in rats at low alcohol concentrations, but fructose increases alcohol drinking at high alcohol concentrations. We found that blocking MCH signaling decreased cocktail drinking, particularly for male rats at higher alcohol concentrations. However, how the activity of MCH neurons is correlated to these behaviors is unknown. MCH activity has been shown to gradually increase during chow feeding, but MCH activity during sugar or sugar-sweetened alcohol cocktail drinking has been unexplored. Using a combinatorial viral approach, we targeted lateral hypothalamic MCH-positive neurons with a genetically encoded calcium indicator and used fiber photometry to estimate MCH neuronal activity in adult female (n=3) and male (n=2) Wistar rats. Subjects were presented with naturalistic stimuli including a brief auditory stimulus, presentation of a novel object, and a tail touch. Also, rats drank sugar solutions of 10% glucose or fructose, and cocktail solutions of 10% glucose or fructose with 1.25% or 10% alcohol added. Our initial results showed rapid phasic increases in MCH fluorescent signal at the beginning of naturalistic stimuli. MCH signal rapidly increased, peaking at the start of the novel object and tail touch. The signal gradually decreased during presentation of the stimuli. MCH signal also had a rapid rise in signal before each drinking bout for glucose and fructose solutions and for alcohol cocktails containing glucose and fructose at both 1.25% and 10% alcohol. Female and male rats both showed an MCH response to stimuli and drinking behavior; sex differences will be discussed at the conference. These findings suggest that MCH neurons are active during sensory stimuli and before the start of sugar and sugar-sweetened cocktail drinking, which may have implications for FAB drinking in humans.

Disclosures: I.R.K. Kuebler: None. J. Chin: None. J. Vollan: None. M. Suarez: None. K.T. Wakabayashi: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.05/U1

Topic: G.08. Food and Water Intake and Energy Balance

Support: SECIHTI Grant CF-2023-I-355

Title: TRH signaling in the nucleus accumbens mediates the anorexigenic effect of central amygdala-stimulation

Authors: *I. HERNÁNDEZ¹, K. SIMON², V. M. MAGDALENO-MADRIGAL³, P. DE GORTARI⁴;

¹Dirección de Investigaciones en Neurociencias, Inst. Nacional de Psiquiatría Ramón de la Fuente Muñiz INPRFM, Ciudad de México, Mexico; ²Dirección de Investigaciones en Neurociencias, Inst. Nacional De Psiquiatría Ramón De La Fuen, Mexico DF, Mexico;

³Dirección de Investigaciones en Neurociencias, Inst. Nacional De Psiquiatría Ramón de la Fuente Muñiz, Ciudad De México, Mexico; ⁴Dirección de Investigaciones en Neurociencias, Inst. Nacional De Psiquiatría, Mexico DF, Mexico

Abstract: The central nucleus of the amygdala (CeA) is involved in modulating feeding behavior. However, the peptidergic nature of the involved neurons and their efferent projecting brain regions, remain unclear. Here we investigated whether the anorexigenic effect of CeA stimulation is mediated by thyrotropin-releasing hormone (TRH) signaling into the nucleus accumbens (NAc). Male Wistar rats (n=4/group) stereotactically implanted with stainless steel electrodes in CeA (AP-1.8 mm, ML +3.5, DV -8.0 from Bregma) were sham manipulated or stimulated for 7 consecutive days using a modified kindling protocol (1-s train of 1-ms biphasic square wave pulses at a frequency of 60 Hz ETC). After 7 days and following a 48-h fasting period, rats were stimulated one last time 5 h prior to food reintroduction. Food intake was quantified at 1h and 2h post-refeeding. CeA-stimulated rats reduced their food consumption in 30% vs. sham controls after 2 h (mean $\pm$ SEM: 2 h, 11.3 $\pm$ 0.22 vs. 7.9 $\pm$ 0.91 g); two-way ANOVA, stimulus *p<0.05; Holm-Sidak: 1 h *p<0.05, 2 h **p<0.01). After sacrificing the animals, brains were extracted, frozen and the NAc dissected to evaluate TRH content by Western blot and TRH mRNA expression in amygdalar nuclei of slices by in situ hybridization. We found 145% elevation of TRH levels in the contralateral NAc of stimulated animals (0.732 $\pm$ 0.057 vs. 1.853 $\pm$ 0.319 arbitrary units; two-way ANOVA, stimulus *p<0.05; Holm-Sidak: Contralateral *p=0.0173) and a higher percentage of TRH mRNA positive cells in amygdalar anterior and pyriform cortices and medial ventral anterior nucleus. In paraformaldehyde perfused brains of a different set of stimulated or sham groups (n=4/group), we also evaluated TRH content by immunohistochemistry in 30 μ m width slices of the NAc; we localized the TRH signal predominantly on the posterior shell region of the NAc (AP+ 0.084, ML -1, DV- 7) adjacently to the lateral ventricle. Importantly, type 1-TRH receptor knockdown via a unilateral stereotaxic injection of antisense phosphorothioated-oligonucleotides (AsODN or MM 10 μ g/ μ l/day for three days before sacrifice) in the NAc shell (AP +1.4 ML -1, DV- 7) of stimulated rats, attenuated the CeA stimulation-induced anorexigenic effect in the 2 h refeeding; a 30% reduction in the TRH-R1 mRNA expression was observed in the NAc of AsODN-stimulated rats when evaluated by RT-PCR and qPCR (two-way ANOVA, *p<0.05; Sidak post hoc: p<0.05) vs mismatch-injected rats. Our results suggested that CeA stimulation-induced anorexic behavior is mediated, at least in part, by TRH signaling into the NAc. This identifies a novel pathway linking limbic circuitry to homeostatic regulation of feeding behavior.

Disclosures: I. Hernández: None. K. Simon: None. V.M. Magdaleno-Madrigal: None. P. De Gortari: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.06/U2

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant GR1065850

Title: Characterization of the functional and structural connectivity of melanin-concentrating hormone neurons in the zona incerta and lateral hypothalamus.

Authors: *J. CAI, S. E. KANOSKI;
USC, Los Angeles, CA

Abstract: Melanin-concentrating hormone (MCH) is a neuropeptide that promotes positive energy balance. MCH-producing neurons are located exclusively in the zona incerta (ZI) and the lateral hypothalamic area (LHA), yet the anatomical and functional distinctions between these two MCH neuron populations are poorly understood. Here we use complementary approaches to anatomically and functionally define the respective downstream targets of ZI and LHA MCH neurons. To determine the monosynaptic projections of ZI MCH neurons distinct from those neighboring in the LHA, rats received unilateral infusion of an anterograde neural tracer under the control of a selective MCH promoter (pMCH AAV serotype 1) into the ZI. Whole midbrain and forebrain analyses systematically quantified axonal density from ZI MCH neurons using the Axiome C platform, with density represented in a 2D flatmap format to facilitate comparative analysis of projections. To determine the functional targets of ZI vs. LHA MCH neurons, we next employed autoradiographic 2-DG-based metabolic brain mapping to identify regions showing either no change (resting state), increased, or decreased glucose uptake following chemogenetic activation of ZI MCH neurons. In rats that received bilateral infusion of a pMCH AAV expressing the excitatory chemogenetic receptor selectively into ZI MCH neurons, the chemogenetic ligand deschloroclozapine or its vehicle was administered followed by radiolabeled 2-deoxy-D-glucose. This approach allows for subsequent visualization of whole midbrain and forebrain glucose metabolism in coronal sections as a proxy for neural activity following ZI MCH neuron activation, followed by Axiome C-based 2D flatmap representation for parallel comparison with monosynaptic projections. Results reveal that ZI MCH neurons have widespread monosynaptic projections, including dense input to the periaqueductal gray (PAG) and the ventral tegmental area (VTA). Further, activation of ZI MCH neurons leads to both neural activation (e.g., nucleus accumbens, PAG, VTA) and inhibition (e.g., basolateral amygdala, dorsal dentate gyrus). This combination of approaches allows for systematic comparison of structural and functional targets of specified neuron populations, and reveals widespread targeting from ZI MCH neurons. Analogous anatomical and functional analyses of LHA MCH neuronal projections are currently ongoing.

Disclosures: J. Cai: None. S.E. Kanoski: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.07/U3

Topic: G.08. Food and Water Intake and Energy Balance

Support: CONAHCyT Ciencia de Frontera CF-2023-I-355 (PG)

Title: Time restricted feeding as a non-pharmacological strategy for chronic stress-related obesity and hyperphagia in rodents

Authors: *O. DIAZ-BARRIGA-PONCE^{1,2}, C. GARCIA-LUNA¹, E. ALVAREZ¹, E. ESPITIA-BAUTISTA¹, P. DE GORTARI¹, P. SOBERANES-CHAVEZ¹;

¹Mol. Neurophysiol., Natl. Inst. of Psychiatry, Mexico City, Mexico; ²Escuela de Dietética y Nutrición, ISSSTE, Mexico City, Mexico

Abstract: The overconsumption of palatable food (PF) and chronic stress (CS) can alter the circadian rhythms and promote obesity, a worldwide health concern. Satiety in rodents is associated with the hyperactivation of a neural circuit involving melanocortin-4 receptor (MC4R)-expressing neurons of the paraventricular nucleus (PVN) that project to calcitonin gene-related peptide (CGRP)-non-expressing parabrachial nucleus (PBN) cells; the inhibition of this circuit is linked to the development of hyperphagia. The chronic stress-induced PF overconsumption might be related to an altered functioning in the PVNMC4R-PBN circuit. Time restricted feeding (TRF) has beneficial effects on metabolism such as reducing food intake and body weight, even in chronically stressed rats, here we characterize a possible activating effect of this regime on the PVNMC4R-PBN circuit in 2-week chronic stress-induced hyperphagic rats. We subjected 32 male rats to CS (isolation-housing) (n=16) or control conditions (pair-housing) (n=16) for 2 weeks in inverted light-dark cycle; then, rats were divided in 4 groups: TRF groups (control (TRF-C) or stressed (TRF-S) rats, n= 8rats/group) with food offered only during 8 h in the activity phase (9:00-17:00 h) and all-day (ADA) groups with food available 24 h (control (ADA-C) or stressed (ADA-S) rats, n=8/group). All groups had ad libitum access to chow and PF (chocolate milk) for the six experimental weeks. We registered the daily consumption of chow and PF, and weekly body weight. After the 6th week, animals were euthanized by trans-cardiac perfusion with paraformaldehyde, brains were frozen, sliced and kept in a cryoprotectant solution until evaluating neuronal activity using immunofluorescence for c-Fos/MC4R, and c-Fos/TRH in the PVN; and c-Fos/CGRP in the PBN. Independently of stress exposure, TRF schedule promoted 48% and 39% less body weight gain in weeks 3 and 4, respectively; 19% and 20% lower total energy intake. Also, TRF reduced PF intake along the experiment, reaching 69% vs ADA groups in week 4. CS rats had the lowest activation of PVNMC4R neurons, showing lower co-expression with c-Fos. The PVNMC4R expressing neurons of TRF rats increased vs. ADA group, as well as their co-localization with c-Fos. These preliminary results suggest that stress promoted dysfunction in PVNMC4R neurons

that could be associated with PF hyperphagia and overweight. Interestingly, TRF reversed CS alterations, showing that PVNMC4R neurons are more active in animals with decreased food intake and body weight. These results support TRF as a promising strategy for obesity, that resets neuronal circuits and restore a healthy regulation of energy homeostasis.

Disclosures: O. Diaz-Barriga-Ponce: None. C. Garcia-Luna: None. E. Alvarez: None. E. Espitia-Bautista: None. P. De Gortari: None. P. Soberanes-Chavez: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.09/U5

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant R01DK115503

Title: Melanocortin-3 Receptor Expression in Ventral Tegmental Area Neuron Subtypes

Authors: *M. MANIERI, A. G. ROSEBERRY;
Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: The central melanocortin-3 receptor (MC3R) is an essential component in the neural regulation of feeding. MC3Rs are highly expressed in the ventral tegmental area (VTA), which is the primary neural circuit controlling reward behavior. The VTA, including neurons expressing the MC3R, also plays an important role in multiple aspects of feeding and is a heterogenous brain nucleus containing both dopamine and γ -aminobutyric acid (GABA) neurons, as well as recently identified glutamate neurons. Although dopamine has been widely implicated in multiple aspects of feeding, the involvement of VTA GABA and glutamate neurons in feeding behaviors is less characterized. While MC3Rs in the VTA are expressed in dopamine neurons, the extent of MC3R expression in other VTA neuron subpopulations remains to be elucidated. Thus, in order to understand the function of VTA MC3Rs, it is important to identify which individual neuronal subtypes in the VTA express MC3Rs. In these studies, we used two approaches to identify the distribution of MC3Rs in dopaminergic, GABAergic, and glutamatergic neurons in the VTA of male and female adult mice. First, we used transgenic mice expressing distinct fluorescent markers in MC3R and GABA or glutamate neurons, in combination with immunohistochemistry for tyrosine hydroxylase (a marker for dopamine neurons). Second, MC3R mRNA in distinct VTA neuron subtypes was quantified in wildtype mice using RNAscope *in situ* hybridization. For both experiments, confocal images were obtained throughout the rostral-caudal extent of the VTA, and the distribution of MC3R expression in the different neuron subtypes was quantified. Preliminary results confirm that MC3R are expressed on both dopaminergic and non-dopaminergic neurons. Specifically, 70% of MC3R neurons are dopaminergic, 1% are GABAergic (based on co-localization with the

vesicular GABA transporter), while 10% are glutamatergic, and 10% co-express both dopamine and glutamate. Determining the distribution of MC3R-expressing VTA neurons among these three neuronal populations is a crucial first step in understanding how changes in VTA MC3R neuronal activity differentially affect VTA circuits and their role in regulating feeding and other behaviors.

Disclosures: M. Manieri: None. A.G. Roseberry: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.10/U6

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant GM127251 to AMK
HHMI PERSIST Brain Mapping & Connectomics Lab
MERITUS Award to ARAM (Campus Office for Undergraduate Research/Office of Provost)
SMART MIND to ARAM (NIH Grant R25DA033613)
UTEP Research Incentive Fund (AMK)
Department of Biology, Lab Instructional Funds
UTEP Research Incentive Fund (AMK)

Title: High-resolution neuroanatomical analysis of the calcitonin gene-related peptide (CGRP) and substance P (SP) chemoarchitecture in the lower brainstem

Authors: *K. N. BANUELOS¹, J. PALACIOS², A. A. MIN², A. M. BLAKE², A. R. ARVIZU MORALES², G. P. TAPIA², S. BALIVADA², A. M. KHAN²;

¹Biol. Sci., Univ. of Texas at El Paso, Vinton, TX; ²Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: Calcitonin gene-related peptide (CGRP) and substance P (SP) are neuropeptides involved in the transmission of sensory (especially pain-related) signals. Within feeding-related studies, CGRP and SP are recognized for suppressing appetite and influencing satiety. The hindbrain contains crucial autonomic pathways that integrate visceral sensory input, nociceptive processing, and homeostatic regulation. However, detailed maps of the fiber systems transmitting these signals remain incomplete, hampering effective targeting of these pathways for experimental study. Therefore, we examined the structural interactions of CGRP-containing nerve fibers with substance P-containing elements to investigate the anatomical organization of these two systems in the hindbrain, particularly in the parabrachial nucleus (PB), nucleus of the solitary tract (NTS), medullary reticular nucleus (MDRN), and spinal trigeminal tract (sptV). Utilizing single-label nickel-enhanced immunoperoxidase staining and double-label

immunofluorescence staining, we identified CGRP and SP immunoreactive patterns and localized them to key hindbrain levels of a standardized rat brain atlas (*Brain Maps 4.0*; Swanson, *J Comp Neurol*, 2018) (*BM4.0*). Photomicrographs of immunostained tissue sections were imported into Adobe Illustrator and the varying levels of immunoreactive signal were scored on a *sparse, light, moderate, and heavy* scale. To compare the distribution of immunoreactive densities across a cohort of subjects, we applied a spatial averaging algorithm that revealed distinct zones of CGRP and SP spatial overlap, notably within the PB, MDRN, NTS, and sptV. Colocalization within the same nerve fibers was observed to a lesser degree, suggesting these systems may be mostly separate, yet intricately interwoven. These findings suggest region-specific zones of CGRP and SP convergence, shedding light on how pain and feeding pathways may intersect in this region.

Disclosures: K.N. Banuelos: None. J. Palacios: None. A.A. Min: None. A.M. Blake: None. A.R. Arvizu Morales: None. G.P. Tapia: None. S. Balivada: None. A.M. Khan: None.

Poster

PSTR033: Regulation of Ingestive Behavior and Homeostasis by Neuropeptides and Other Modulators

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR033.11/U7

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Ben and Maytee Fisch Chair in Pharmacy Endowment
Edna Walsh Research Fund.

Title: Effect of Cannabidiol (CBD) Exposure on Lung Epithelial Cells

Authors: *N. M PINHEIRO MENEGASSO, A. AL-SHWEIKY, R. BEAUDOIN, A. K. HAMOUDA;
Univ. of Texas at Tyler, Tyler, TX

Abstract: The medical and recreational use of cannabidiol (CBD), a biologically active and non-psychoactive compound derived from cannabis, has risen significantly in recent years. CBD is available in multiple dosage forms and is frequently consumed via vaping devices (CBD pens). Inhalation leads to a rapid increase in CBD levels in the bloodstream, producing immediate effects. However, exposure to high concentrations of inhaled CBD may induce cytotoxic effects on lung epithelial cells. This study aimed to evaluate CBD toxicity and its impact on key inflammatory mediators in lung cells. Human lung epithelial cells (A549 CCL-185) were cultured and treated with increasing concentrations of CBD (0.3-10 µg/mL) for 6, 12, 18, and 24 hours. Cell viability was determined using the CyQUANT MTT assay and gene expression for TNF- α , IL-1 β , TLR4, and acetylcholine receptors were analyzed by RT-qPCR. Cell viability following CBD exposure was concentrations and time dependent. The minimum concentration of CBD and duration of exposure that resulted in reduction of cell viability were 6 µg/mL for 24

hours and 10 µg/mL for 12 hours. Preliminary data showed that 4-hour exposure to 10 µg/mL CBD reduced TNF-α and IL-1β expression compared to the control. However, longer exposure (18 hours) to 10 µg/mL CBD led to increase in TNF-α, IL-1β, and TLR4 expression. Additionally, 18-hour CBD exposure resulted in reduced gene expression of α4 and α7 nicotinic acetylcholine receptors. Studies using pharmacological agents modulating CB1 and CB2 cannabinoid receptors are ongoing to elucidate the mechanisms of CBD's effects on inflammatory pathways and cholinergic receptors in lung epithelial cells.

Disclosures: N. M Pinheiro Menegasso: None. A. Al-Shweiky: None. R. Beaudoin: None. A.K. Hamouda: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.01/U8

Topic: H.03. Motivation

Support: 25-BR-02-02
25-BR-05-02
RS-2024-00460958
RS-2024-00332645
RS-2024-00508718

Title: Epigenetic reprogramming of stress-related circuits reveals sex-specific vulnerability to depressive-like and cognitive impairments

Authors: *J. S. KIM¹, T.-E. KIM³, T. LEE², J. L. ABLES⁵, J. KOO⁴;

¹Emotion, Cognition & Behavior research group, ²Lab. Animal Ctr., Korea Brain Res. Inst., Daegu, Korea, Republic of; ³Emotion, Cognition & Behavior Res. Group, ⁴Emotion, Cognitive & Behavior Res. Group, Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; ⁵Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Emerging research highlights critical sex differences in cognitive impairment associated with depression, though the underlying mechanisms remain poorly understood. Our study identifies DYRK1A, a kinase traditionally associated with intellectual disability, as a key contributor to these sex-specific differences. Through the analysis of previous clinical data, we found that DYRK1A is overexpressed in the frontal lobes of both male and female patients with depression. Using advanced imaging and genetic techniques in mice, we demonstrate that DYRK1A activation induces depressive behaviors and cognitive deficits, with differential effects based on sex. In male mice, DYRK1A overexpression exacerbated both emotional and cognitive symptoms, whereas inhibition or knockdown of DYRK1A produced antidepressant-like effects. Notably, DYRK1A overexpression in males drives serotonin degradation in the prefrontal cortex by recruiting RNA polymerase II to the MAO-A promoter, a mechanism absent in females. In

contrast, female mice exhibited depressive behaviors following DYRK1A overexpression, but without the associated cognitive deficits, suggesting a distinct biological pathway in female depression. These findings reveal a novel, sex-specific role for DYRK1A in depression, offering new insights into the biological underpinnings of cognitive impairment and highlighting potential targets for sex-specific therapeutic interventions.

Disclosures: J.S. Kim: None. T. Kim: None. T. Lee: None. J.L. Ables: None. J. Koo: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.02/U9

Topic: H.03. Motivation

Support: NRF Grant 2021R1A2C2094627
NRF Grant RS-2024-00460958
NRF Grant 2024-00508718

Title: Autism-like behavior in *Agbl4* knockout mice and rescue by enhanced prefrontal inhibitory neurotransmission

Authors: *E. KIM¹, J. LEE², S. KANG³, D.-S. KANG⁴, Y. KO⁴, J. KOO⁵, T.-Y. CHOI⁶;
¹Korea Brain Inst., Daegu, Korea, Republic of; ²Daegu Gyeongbuk Inst. of Sci. and Technol., Daegu, Korea, Republic of; ³Kyungpook Natl. Univ., Daegu, Korea, Republic of; ⁴Korea Brain Res. Inst., Daegu, Korea, Republic of; ⁵Emotion, Cognitive & Behavior Res. Group, ⁶Emotion, Cognition & Behavior Res. Group, Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication, along with restricted and repetitive patterns of behavior. ASD arises from diverse neurobiological factors that disrupt brain development, leading to broad impairments in social functioning, language, cognition, emotional regulation, and sensory processing. Recent genetic studies have implicated *Agbl4*, which encodes cytosolic carboxypeptidase 6 (CCP6), as a potential ASD-associated gene due to its role in tubulin deglutamylation and microtubule regulation. However, the functional significance of *Agbl4* in the brain, particularly in regions involved in social behavior such as the medial prefrontal cortex (mPFC), remains largely unknown. In this study, we investigated the behavioral and neurophysiological consequences of *Agbl4* deficiency using *Agbl4* knockout (KO) mice. Through a multi-modal approach combining behavioral assays, immunohistochemistry, electrophysiological recordings, and transcriptomic analyses, we demonstrate that loss of *Agbl4* leads to synaptic and circuit-level disruptions in the mPFC, accompanied by impairments in social behavior. Furthermore, we identify potential therapeutic strategies targeting the observed pathophysiological changes. These findings confirm that *Agbl4* as a key molecular factor in the regulation of mPFC-dependent social behavior and suggest that its dysfunction may contribute to

the pathophysiology of ASD. While ASD is widely recognized as a polygenic disorder, our results underscore the importance of *Agbl4* in shaping core behavioral domains relevant to the disorder, offering a potential target for therapeutic intervention.

Disclosures: E. Kim: None. J. Lee: None. S. Kang: None. D. Kang: None. Y. Ko: None. J. Koo: None. T. Choi: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.03/U10

Topic: H.03. Motivation

Support: 25-BR-02-02
25-BR-07-01
RS-2024-00460958
RS-2024-00332645
RS-2024-00508718

Title: Chronic unpredictable stress-induced in Feeding Behavior and Emotional Phenotypes via Glp1R and MC4R Downregulation in the Nucleus Accumbens

Authors: *Y. KO^{1,3}, J. KIM⁴, T. SON², J. KOO⁴;

²Korea Brain Bank, ¹Korea Brain Res. Inst., Daegu, Korea, Republic of; ³Kyungpook Natl. Univ., Daegu, Korea, Republic of; ⁴Emotion, Cognitive & Behavior Res. Group, Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of

Abstract: Stressful events are well-established risk factors for psychological disorders, particularly depression. Nevertheless, a substantial subset of individuals demonstrate resilience, maintaining stable psychological functioning despite repeated exposure to adverse stressors. While stress-induced symptoms such as anhedonia, dysregulated feeding behaviors, and behavioral despair are frequently observed, the precise synaptic and molecular mechanisms underlying these diverse phenotypes remain largely unknown. In this study, we examined the effects of chronic unpredictable stress (CUS) on behavior and gene expression in an inbred mouse model. Mice exposed to CUS exhibited significant behavioral alterations, including reduced sucrose preference (anhedonia), abnormal feeding patterns, and increased behavioral despair. Transcriptomic analysis using RNA sequencing revealed stress-specific gene expression changes in the nucleus accumbens (NAc), a key brain region involved in motivation and emotional regulation. Notably, we observed significant downregulation of glucagon-like peptide-1 receptor (Glp1R) and melanocortin 4 receptor (MC4R) genes in the NAc of stressed mice. Both genes play essential roles in appetite regulation, energy balance, and mood modulation. These findings suggest that stress-induced suppression of Glp1R and MC4R signaling within the NAc may contribute to disrupted feeding behavior and emotional dysregulation. Our study

highlights a potential molecular pathway linking chronic stress to neurobehavioral outcomes and identifies promising targets for intervention in stress-related disorders.

Disclosures: Y. Ko: None. J. Kim: None. T. Son: None. J. Koo: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.04/U11

Topic: H.03. Motivation

Support: NIAAA Intramural Research Program
Center on Compulsive Disorders

Title: Amygdala-striatal regulation of punished decision-making

Authors: *P. T. PIANTADOSI¹, A. HOLMES²;

¹Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD; ²NIH/NIAAA, Rockville, MD

Abstract: Cost/benefit analyses are disturbed in substance use disorders and have been suggested to be mediated by interactions between cortico-limbic-striatal circuits. Within these circuits, the basolateral amygdala (BLA) has been shown to be critical for aversive costs like punishment to produce flexible changes in actions. Yet, it remains unclear how the BLA facilitates such flexibility. Here, we used in vivo 1-photon imaging, fiber photometry, and optogenetic manipulation in male mice to detail BLA function during cost/benefit decision making, identifying a BLA to nucleus accumbens shell (NAcSh) projection that contributes to action flexibility. Mice were first trained to discriminate between one reward port that delivered a large amount of milkshake reinforcement, and another that delivered a small amount. Mice then received risky decision-making task (RDT) sessions whereby selection of the large reward was associated with a minor footshock that ascended in likelihood across three trial blocks (0, 50, and 75% probability). Selection of the small reward option was never punished. Throughout training and RDT sessions, GCaMP6-based fluorescence was imaged using microendoscopic 1-photon imaging. During reward magnitude training, subsets of BLA neurons displayed consistent responses to rewarded events during the pre-choice and post-choice period, while others developed or lost responsivity over multiple days of training. The introduction of punishment risk during the RDT dramatically affected behavior: mice deliberated longer prior to making a choice, displayed behaviors characteristic of anxiety-related indecision, and gradually shifted their choice towards the small, safe reward. This shift was associated with changes in BLA neuron activity: for example, many neurons encoded footshock punishment, with most being recruited from a pool of cells that were not reward-excited. We next assessed whether signaling in a discrete BLA-NAcSh pathway was sensitive to risk and causally related to flexibility. Using projection-specific fiber photometry and 1-photon imaging, we observed that the BLA-NAcSh population was less sensitive to footshock punishment than the overall BLA population, but

pathway activity preceding actions was significantly inhibited by punishment risk. To test whether this inhibition causally contributed to actions, we optogenetically excited BLA terminals in the NAcSh, which produced a robust increase in risk-seeking. These data provide novel insight into the manner in which BLA processes punishing information, with ongoing experiments exploring further differences in projection-specificity and transcriptional profile.

Disclosures: P.T. Piantadosi: None. A. Holmes: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.05/Web Only

Topic: H.03. Motivation

Title: Zona incerta neurons control compulsive eating

Authors: *W. SHEN;
shanghaitech university, Shanghai, China

Abstract: Binge eating disorder (BED) is characterized by recurrent episodes of excessive food consumption with impaired control, often accompanied by compulsive eating despite adverse consequences. Using an intermittent high-fat diet (HFD) model, we identified the activation of the anterior zona incerta (aZI) as a key neural correlate of binge eating. Optogenetic activation of aZI neurons robustly promoted binge eating, pinpointing this region as a functional hotspot. Single-cell sequencing and behavioral analyses revealed specific neuronal markers associated with binge eating. Activation of these marker-defined neurons induced compulsive food-seeking and consumption, overriding negative deterrents such as electric shocks and aversive taste. Furthermore, circuit mapping implicated dopamine system engagement in compulsive eating behavior. These findings elucidate a mechanistic framework for ZI-mediated compulsive behaviors in BED, offering novel insights into its pathophysiology and potential therapeutic targets.

Disclosures: W. shen: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.06/U12

Topic: H.03. Motivation

Support: NIH Grant MH137085

Title: A uniform neuronal mechanism for motor and motivational control: evidence from multi-contact recordings throughout prefrontal cortex

Authors: *J. G. ELSEY¹, V. STUPHORN²;

¹Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, SC; ²Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: In everyday life, we must often interrupt or suppress a behavior in favor of others that are more appropriate in the current circumstances or in accordance with our long-term goals. Behavioral control is a fundamental component of executive control that is responsible for the suppression of actions, thoughts, and emotions. Two key aspects of behavioral control are response inhibition (motor domain) and self-control (motivational domain). Response inhibition is the ability to deliberately stop a prepared motor response. Self-control is the ability to inhibit self-defeating behavior in the face of temptation. Human imaging studies have identified several prefrontal regions that are active during tasks requiring these two forms of behavioral control, however it is unknown whether the neural mechanisms that determine the success or failure of response inhibition or self-control are shared or distinct. Specifically, it is not known whether motor and motivational control is mediated through a common neural circuit or in parallel across different functional domains. To address this, we recorded single-unit neurons using linear vector arrays from Frontal Eye Field (FEF), Supplementary Eye Field (SEF), Dorsolateral Prefrontal Cortex (DLPFC) and Ventrolateral Prefrontal Cortex (VLPFC) in macaques performing saccade stop-signal (countermanding) and self-control tasks. Both tasks provide specific criteria within discrete epochs that neural activity must satisfy to be causally linked to either mechanism of behavioral control. We identified FEF as a region of interest because of its known role in oculomotor response inhibition, but not motivational control. In contrast, SEF has been found to play a role in motivational control, but not response inhibition. VLPFC and DLPFC have been implicated in imaging studies of response inhibition and self-control, however these findings have yet to be replicated at single-unit resolution. Thus, this study aims to compare the dynamic, circuit-level mechanisms of response inhibition and self-control within and across each brain region with greater spatial and temporal resolution. Using a Poisson GLM, we find task-invariant control signals biasing performance in all four regions. Specifically, subsets of neurons encoded the likelihood of successful motor inhibition in the stop-signal task and successful commitment to the initial choice in the face of suboptimal temptation in the self-control task. In summary, we find that motor-related activity in prefrontal regions can be modulated by the animal's level of self-control, suggesting that motor and motivational control may share a common neural circuit.

Disclosures: J.G. Elsey: None. V. Stuphorn: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.07/U13

Topic: H.03. Motivation

Support: ZIAAA000550

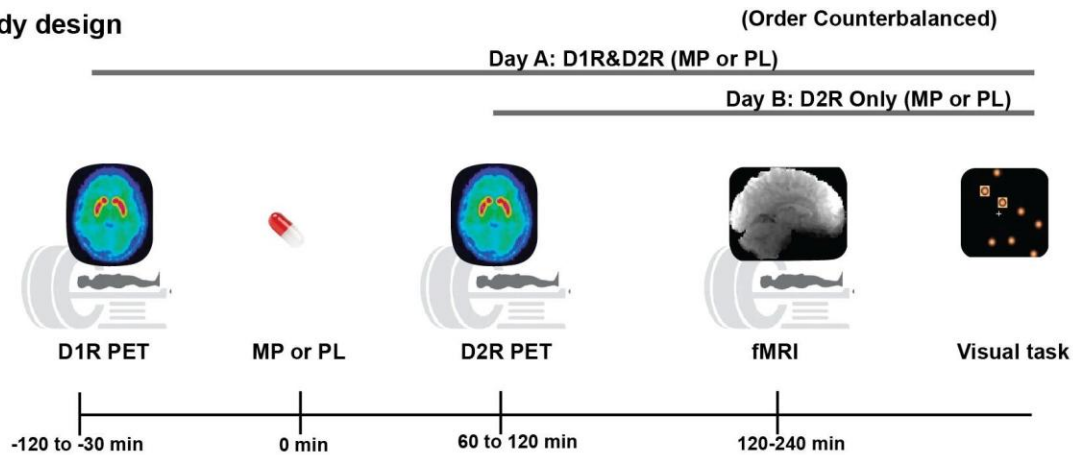
Title: Methylphenidate promotes a frontoparietal-dominant brain state improving cognitive performance

Authors: *W. YAN¹, N. D. VOLKOW²;

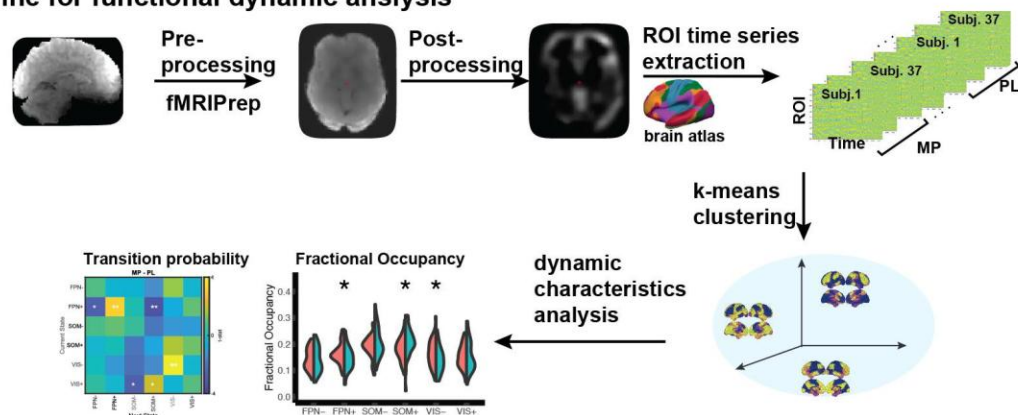
¹Natl. Institutes of Hlth., Bethesda, MD; ²NIH, Natl. Inst. On Drug Abuse, Gaithersburg, MD

Abstract: Methylphenidate (MP) is a widely used stimulant medication for the treatment of attention deficit hyperactivity disorder that enhances brain dopamine signaling and improves attention. However, how dopamine stimulation alters brain state dynamics to support improved attention during task performance is still unclear. To address this, we employed a multimodal neuroimaging approach combining positron emission tomography, functional magnetic resonance imaging, and behavioral tasks, to discover associations between dopamine signaling, brain dynamics, and cognition. Multimodal images were collected from 37 healthy adults under a single-blind, counterbalanced, placebo-controlled crossover study. Dynamic functional analysis was used to compare the alterations in dynamic features of brain states before and after MP. Subsequently, we analyzed the correlation between these brain state changes and baseline striatal D1 and D2 dopamine receptor (D1R, D2R) availability. We also examined alterations in dynamic brain states and their effects on visuospatial tasks. The results showed that MP primarily affected frontoparietal-dominant activated (FPN+), somatomotor-dominant activated (SOM+), and visual-dominant suppressed (VIS-) brain states. Specifically, the dwell time and fractional occupancy exhibited significant increases within the FPN+ and VIS- and an opposite trend within the SOM+. Furthermore, the increase of dwell time in FPN+, which was positively correlated with baseline striatal D1R availability, was also associated with quicker response in the 2-ball-track task, but not significantly for the 3-ball-track task. The findings suggest that MP's enhancement of brain states with FPN+ and VIS- while decreasing SOM+, in part through D1R signaling might underlie MP's improvement of attention for low demanding tasks in healthy populations.

(A) Study design



(B) Pipeline for functional dynamic analysis



Disclosures: W. yan: None. N.D. Volkow: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.08/U14

Topic: H.03. Motivation

Support: NIH DK134804

Title: Short-term exposure to obesogenic diets induces transient motivational deficits in mice

Authors: *L.-C. CHAO¹, B. A. MATIKAINEN-ANKNEY²;

¹Psychology department, Rutgers University–New Brunswick, Piscataway, NJ; ²Psychology, Rutgers Univ. Behavioral and Systems Neurosci., Highland Park, NJ

Abstract: Obesity affects more than 1/3 of Americans, and there is yet no cure. Modern lifestyles, characterized by the overconsumption of calorie-dense foods, have driven obesity rates to skyrocket in recent decades, and obesity now stands to eclipse smoking as the leading cause of preventable death in the US. This suggests obesity is tied to neurobiological changes driving persistent behavioral deficits. However, while extensive studies have focused on the prolonged effect of high-calorie diets, it is still unknown how rapidly such behavioral phenotypes arise. In this study, we investigated whether short-term (three-day) ad libitum consumption of high-fat or high-sugar diets induced obesity-like motivational deficits in male and female mice in a nose-poking operant task for sucrose pellets and how long the deficits persisted. Male and female mice were trained on progressive ratio (PR) nose poking tasks for sucrose pellets, then exposed to three days of either a high-fat diet, high-sucrose or high-glucose diet, isocaloric high-fat diet, or standard chow. Motivation was reassessed immediately following diet exposure and again four days later. Daily weight is taken throughout the entire experiment to track the weight difference before and after the three days of diet exposure. The data showed that three-day ad libitum exposure to a high-fat diet led to significant weight gain and decreased the response towards sugar pellets in male and female mice immediately after diet exposure, which did not persist four days after exposure. On the other hand, three-day ad libitum exposure to high sucrose or high-glucose diets did not significantly change weight or decrease responding, nor did exposure to an isocaloric amount of high-fat diet. These results suggest that obesity-linked deficits in motivation are tied to diets high in fat and potentially increased adiposity.

Disclosures: L. Chao: None. B.A. Matikainen-Ankney: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.09/U15

Topic: H.03. Motivation

Support: NIH grant ZIA MH002928
Brain and Behavior Foundation Grant 32825

Title: An embodied architecture for reinforcement learning in the primate brain

Authors: *F. GIARROCCO¹, B. B. AVERBECK²;
¹NIMH, NIH, Bethesda, MD; ²NIMH/NIH, Bethesda, MD

Abstract: The corticobasal ganglia (CBG) system is a core circuit motif in the brain, essential for learning, motivation, and action. This system has traditionally been described according to a dorsal-ventral dichotomy, reflecting anatomical pathways and functional specializations. Dorsal circuits, including cortical networks and their projections to the dorsal striatum, have particularly expanded in primates along with the emergence of specialized motor systems (e.g., reaching). These circuits encode both action parameters and the value of the actions they specify. In

contrast, ventral circuits, including the ventral striatum (VS) and its connections to motivational regions such as the amygdala, are evolutionarily conserved and have been considered the seat of single, motor system-invariant value signals. This anatomical differentiation has shaped theoretical frameworks in reinforcement learning (RL), promoting the dominant view that a single, abstract state-value signal computed in ventral “motivational” structures guides learning across motor systems. This view is formalized in the actor-critic model, where a centralized “critic,” typically localized to the VS, encodes reward prediction errors and state-value signals to update an “actor,” usually identified within dorsal circuits, responsible for implementing motor policies. However, the specialization of motor systems in primates raise the hypothesis that RL may not rely on a single, motor system-invariant value signal, but on value representations embedded within motor systems. In a recent study, we showed that inactivation of amygdala and VS produces motor system-specific deficits in RL, challenging the assumption of a single value system. Building on this, we are conducting large-scale recordings across the CBG system, including premotor and prefrontal cortex, caudate, putamen, medial and lateral VS, globus pallidus, and amygdala, while monkeys perform an RL task requiring either saccades or reaching. Preliminary analyses performed on >2500 neurons recorded over 30 sessions reveal that stimulus- and action-value are represented in a distributed, motor system-specific manner. Crucially, values computed within motivational regions reflect the motor system engaged. These findings challenge the foundational assumption of a single value representation and motivate a conceptual shift in how we conceive of RL in the brain. We propose an embodied model, in which value is not computed by a single system but constructed within motor systems. In this framework, value emerges within action-related circuits, producing neuronal representations defined by the motor systems that generate them.

Disclosures: F. Giarrocco: None. B.B. Averbeck: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.10/U16

Topic: H.03. Motivation

Support: NIH Grant ZIA MH002928 (BA)

Title: Motivation and state value coding across limbic circuitry in the non-human primate

Authors: *D. BURK, B. B. AVERBECK;
NIMH/NIH, Bethesda, MD

Abstract: Deficits in motivation are a core feature of depression and other psychiatric illnesses. The limbic system has been implicated in both reinforcement learning and motivation, but in many paradigms these processes are confounded, obscuring how brain areas might represent changes in motivation. We developed a token task and computational model that examine these

processes in a separable way. In the task, two rhesus monkeys learned to choose images that earn symbolic reinforcers (blue or green tokens). Over multiple trials, the monkeys accumulated tokens that were periodically exchanged for primary rewards: water (preferred) or mint-flavored water (non-preferred). The model provides moment-to-moment estimates of *state value, which fluctuate due to changes in future expected reward during the task*. We then recorded simultaneously from the ventral striatum (VS), ventral pallidum (VP), lateral hypothalamus (LH), insular cortex (InCtx), and amygdala (Amyg) using linear multielectrode arrays. Preliminary analyses of the dataset reveal representation of model-derived state value in every region, with the strongest modulation in VP. The monkeys' motivation was further probed by contrasting completed trials with abort trials. Dynamics analyses suggest that computations are less contracting on abort trials. These differences arise early in the trial, before overt disengagement from the task. By linking computational estimates of motivational state to circuit-level dynamics, this study begins to map how limbic networks integrate internal state with task context and offers new targets for understanding changes in motivation.

Disclosures: D. Burk: None. B.B. Averbeck: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.11/V1

Topic: H.03. Motivation

Support: R21MH131900

Title: Effects of OFC microstimulation on expectation updating

Authors: *J. A. CHARBONNEAU¹, E. L. RICH^{1,2};

¹Ctr. for Neural Sci., New York Univ., New York, NY; ²Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Efficient guidance of motivated behavior requires an organism to constantly generate and update expectations about dynamic environments. The maintenance of incorrect expectations in the face of new information hinders the generation of contextually appropriate behaviors—a core feature across many neuropsychiatric conditions. Here, we sought to determine the causal contribution of one brain region often implicated in the generation of affective expectations—the orbitofrontal cortex (OFC)—to expectation updating. We trained one rhesus macaque on a task that allows for quantification of expectation-guided behavior. Initially, the monkey was trained to associate four pictures with fluid rewards of varying putative pleasantness (0.5 mM quinine, water, 75 mM sucrose, and 200 mM sucrose). On each trial, one (forced choice trials) or two (choice trials) pictures were presented, and the monkey made a selection by fixating the image and releasing a touch-sensitive bar. Selections triggered a reward bolus followed by a 4 second instrumental response period in which repeated taps of the bar produced additional small

amounts of the same reward. During testing sessions, a subset of trials resulted in the delivery of a reward which differed from the monkey's expectation. Likewise, electrical microstimulation was delivered to OFC via acutely implanted platinum-iridium electrodes on a subset of trials. Instrumental response updating during mismatch trials with and without stimulation was compared. In some sessions, OFC stimulation facilitated faster response updating. Stimulation during large positive PEs (e.g., expecting quinine and receiving 200 mM sucrose) resulted in significantly more responses early in the response period and stimulation during large negative PEs (e.g., expecting 200 mM sucrose and receiving quinine) resulted in significantly fewer responses, consistent with a disruption of expectations in favor of new sensory information. However, effects across sessions were heterogeneous. In investigating this heterogeneity, we found that "effective" sessions (those where stimulation facilitated faster updating) were characterized by overall lower baseline pupil diameter, slower image selection, and fewer responses. This pattern of results supports the idea that efficacy of OFC microstimulation in modulating expectation updating depends on the animal's baseline physiological state. This work highlights the importance of considering—and, potentially, manipulating—patients' physiological baselines to enhance effectiveness of neuromodulatory therapies for neuropsychiatric disorders.

Disclosures: J.A. Charbonneau: None. E.L. Rich: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.12/V2

Topic: H.03. Motivation

Support: NIH Grant DA058186

Title: Social vs. Drug Reward: Context-Dependent Preference and Behavioral Engagement in Mice

Authors: *T. R. ERICKSON¹, S. R. ISSA¹, D. B. LESTER²;

²Psychology Dept., ¹Univ. of Memphis, Memphis, TN

Abstract: Understanding how competing rewards alter reward-driven behavior may provide insight into mechanisms of addiction vulnerability and potential protective factors. This study compares the efficacy of social and drug rewards in driving reward-related behavior using conditioned place preference (CPP) paradigms. Three separate CPP paradigms were used in male and female C57BL/6J mice: (1) Social vs. Isolation CPP in which one chamber was paired with social interaction and the other with isolation (control), (2) Cocaine vs. Saline CPP in which one chamber paired with cocaine (10 mg/kg, ip) and the other with saline (control), and (3) Cocaine vs. Social CPP in which one chamber was paired with cocaine and the other with social interaction. For each paradigm, we assessed baseline preference, post-conditioning preference,

and behaviors during reward conditioning. Males and females displayed a cocaine place preference in both cocaine CPP paradigms (Cocaine vs. Saline and Cocaine vs. Social); however, in males, cocaine preference was lower when paired against social interaction than when paired against saline. Males also displayed a social place preference in the Social vs. Isolation CPP but not when social interaction was paired against cocaine. Females did not display a social place preference in either condition. Behavioral assessments during reward conditioning sessions revealed increased behavioral activation in the CPP paradigm in which both chambers were paired with salient stimuli. During cocaine conditioning, mice in the Cocaine vs. Social CPP displayed increased distance traveled, higher velocity, and less time immobile compared to those in the Cocaine vs. Saline CPP. Similarly, during social conditioning, mice in the Cocaine vs. Social CPP displayed increased social engagement and interaction compared to those in the Social vs. Isolation CPP. These findings suggest that social interaction can partially offset drug reward in males, highlighting its potential as a protective factor against drug-seeking behavior. The absence of this effect in females underscores the importance of considering sex differences in addiction research and intervention strategies.

Disclosures: T.R. Erickson: None. S.R. Issa: None. D.B. Lester: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.13/V3

Topic: H.03. Motivation

Support: NIH Grant DA058186

Title: Motivational effort for social and drug rewards in mice

Authors: M. VANN-SCOTT, J. DAVIS, A. NAUHRIA, *D. B. LESTER;
Univ. of Memphis, Memphis, TN

Abstract: Maladaptive reward processing is observed in substance use disorder, in which drug rewards overshadow natural rewards such as social interaction. This study aimed to compare the motivational value of drug and social rewards by quantifying the effort mice are willing to exert to obtain each. Using a novel effort-based reward task, male and female C57BL/6J mice were assigned to one of four reward conditions: cocaine (10 mg/kg, i.p.), social interaction with a familiar conspecific, social interaction with a novel conspecific, or no reward. Mice completed two sessions per day for up to nine days, pushing a door of increasing weight (0g to up to 283g) to access the reward chamber. The breakpoint, defined as the highest weight successfully pushed before failure, served as the primary measure of motivation. Mice exerted the most effort for cocaine ($M = 191.4g$, $SE = 7.1$) and familiar social interaction ($M = 193.7g$, $SE = 15.4$), with moderate effort for novel social interaction ($M = 165.4g$, $SE = 13.5$), and the least effort for the no-reward control condition ($M = 132.3g$, $SE = 38.0$). Ongoing analyses of behavior during

reward access sessions aim to further clarify how reward type influences engagement and arousal. These findings demonstrate that familiar social interaction can be as motivating as cocaine under certain conditions.

Disclosures: M. Vann-Scott: None. J. Davis: None. A. Nauhria: None. D.B. Lester: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.14/V4

Topic: H.03. Motivation

Support: University of Notre Dame Initiation Grant

Title: Characterization of learning paradigms for a new vapor delivery drug self-administration device

Authors: J. OLIVER¹, *D. A. LANE²;

¹Neurosci. and Behavior, ²Biol. Sci., Univ. of Notre Dame, Notre Dame, IN

Abstract: Rodent drug self-administration models are superior to experimenter-initiated drug administration because they include the element of choice. However, traditional self-administration techniques have serious complications that hinder their use. Most procedures require vascular catheterization for drug delivery. The surgery is difficult, causes pain that requires analgesics that may confound drug intake studies, it is difficult to maintain catheter patency with repeated trials. In addition, the need for surgery may preclude other types of surgeries needed for research based on ethical animal care considerations. Because of this, vapor delivery models for self-administration have been designed, but current models also have limitations. They fill the entire test chamber with drug vapor, utilizing large quantities of drug solution. The rapid fill and emptying of the entire chamber with vapor is startling to the animal, adding the element of stress. Additional issues include that the animal is placed into a novel test chamber individually and cannot be tested on other behaviors while self-administering the drug. To address these issues, we have developed a patent-pending small and adjustable self-administration insert that can be used in conjunction with other behavioral equipment, such as open field and conditioned place preference apparatuses, or in the mouse's home cage to prevent stress of moving animals. Only a small amount of vapor is released from into the nosepoke region, instead of filling the entire chamber, utilizing a very small amount of drug solution - a critical factor with new experimental drugs. The drug vapor is silently vacuumed away with a hood placed directly over the nosepoke region, preventing vapor infusion into the enclosure. Finally, we included an RFID reader in the design of the device, allowing self-administration studies of multiple animals simultaneously. This allows scientific examination of social behavior on drug intake in rodent models for the very first time. Because this device is newly developed, the critical elements are now being characterized. The study proposed here investigates the

effectiveness of different learning paradigms on drug intake using mice. Different factors affecting nosepoke behavior will be assessed and reported.

Disclosures: **J. Oliver:** None. **D.A. Lane:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); intellectual property rights/patent holder, University of Notre Dame.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.15/V5

Topic: H.03. Motivation

Support: University of Notre Dame CoS SURF

Title: Optogenetic Stimulation of Ventral Tegmental Area GABAergic Neurons and The Development of Addiction

Authors: ***J. RYAN**¹, D. A. LANE², E. RONCK³;

¹Univ. of Notre Dame, Sparta, NJ; ²Dept. of Biol. Sci., Univ. of Notre Dame, South Bend, IN;

³Univ. of Notre Dame, Rogers, AR

Abstract: Illicit drug and prescription medication misuse has greatly increased within the past decades, leading the well-known opioid epidemic to transition into a polydrug overdose crisis. Despite the prevalence of this issue, there are relatively few effective treatment options for substance use disorders (SUDs), suggesting that further research is necessary to better understand the mechanisms behind addiction. Although AMPA receptor-mediated potentiation of ventral tegmental area (VTA) dopamine (DA) neurons is a well-established model of addiction, it fails to explain the dissociation between diminishing rewarding effects of drugs over time and increased drug-seeking behavior. Prior studies suggest that GABAergic interneurons of the paranigral (PN) and parabrachial (PB) VTA are differentially potentiated after drug exposure, suggesting that they may play a key role in the distinction between rewarding effects and drug-seeking behavior, respectively.

This study aims to evaluate the mechanistic difference between the rewarding aspects of a drug and the motivation for a drug. We hypothesize that differential activity of VTA GABAergic interneurons, that control dopamine neuronal activity, in response to drugs of abuse is necessary and sufficient to mediate the gradual waning rewarding effects of drugs but increased desire for the drug (drug seeking/compulsive intake). Using an adeno-associated virus containing a CRE-dependent channelrhodopsin construct stereotactically injected into specific regions of the VTA of VGAT-CRE mice, we will repeatedly activate PN or PB VTA GABAergic neurons through optogenetic light stimulation and investigate changes in cocaine intake, locomotor activity, and conditioned place preference to the light stimulation and/or cross tolerance between light stimulation and cocaine self-administration. Injection site and relative level of regional activation

will be correlated to behavior changes. It is expected that increased PN VTA GABA activation will decrease the rewarding effects of cocaine, which compliments our previous work (Lane et al., 2010; 2011). In contrast, lack of PB VTA GABA activation (vector control) will prevent drug seeking behavior, something that has not been shown before.

Disclosures: J. Ryan: None. D.A. Lane: None. E. Ronck: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.16/V6

Topic: H.03. Motivation

Support: University of Notre Dame CoS SURF

Title: Characterization of blood drug concentration levels from a new vapor delivery drug self-administration device.

Authors: *E. RONCK¹, D. A. LANE², J. RYAN³;

¹Univ. of Notre Dame, Rogers, AR; ²Dept. of Biol. Sci., Univ. of Notre Dame, Notre Dame, IN;

³Univ. of Notre Dame, Sparta, NJ

Abstract: Rodent drug self-administration models are superior to experimenter-initiated drug administration because they include the element of choice. However, traditional self-administration techniques have serious complications that hinder their use. Most procedures require vascular catheterization for drug delivery. The surgery is difficult, causes pain that requires analgesics that may confound drug intake studies, and is difficult to maintain catheter patency with repeated trials. In addition, the need for surgery may preclude other types of surgeries needed for research based on ethical animal care considerations. Because of this, vapor delivery models for self-administration have been designed, but current models also have limitations. They fill the entire test chamber with drug vapor, utilizing large quantities of drug solution. The rapid fill and emptying of the entire chamber with vapor is startling to the animal, adding the element of stress. Additional issues include that the animal is placed into a novel test chamber individually and cannot be tested on other behaviors while self-administering the drug. To address these issues, we have developed a patent-pending small and adjustable self-administration insert that can be used in conjunction with other behavioral equipment, such as open field and conditioned place preference apparatuses, or in the mouse's home cage to prevent stress of moving animals. Only a small amount of vapor is released into the nosepoke region, instead of filling the entire chamber, utilizing a very small amount of drug solution - a critical factor with new experimental drugs. The drug vapor is silently vacuumed away with a hood placed directly over the nosepoke region, preventing vapor infusion into the enclosure. Finally, we included an RFID reader in the design of the device, allowing self-administration studies of multiple animals simultaneously. This allows scientific examination of social behavior on drug

intake in rodent models for the very first time. Because this device is newly developed, the critical elements are now being characterized. The study proposed here investigates the effectiveness of the self-administration device in delivering drug types in vapor form. Measurements of blood drug and metabolite concentrations from mice utilizing the self-administration insert will be reported based on different vapor concentrations, timings, and environment/apparatus placement will be reported.

Disclosures: E. Ronck: None. D.A. Lane: None. J. Ryan: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.17/V7

Topic: H.03. Motivation

Support: NIH R01 DA057292
MH129370
MH129320

Title: Heterogeneity in Somatodendritic Dopamine Signaling in the VTA/SNc during Pavlovian Learning

Authors: *G. STEMMLER¹, A. R. WOLFF², B. T. SAUNDERS²;

²Dept. of Neurosci., ¹Univ. of Minnesota, Minneapolis, MN

Abstract: Dysregulation of brain reward networks that govern learning processes and motivated behavior is a key component of substance use disorders. The ventral tegmental area (VTA) and substantia nigra (SNc) contain dopamine neurons that project throughout the brain and integrate sensory and emotional information to reinforce valenced learning, motivation, and invigoration. Notably, midbrain dopamine neurons are not only regulated by synaptic inputs, but through local dopamine release at somatic and dendritic regions. The *in vivo* temporal dynamics of somatodendritic dopamine release during learning are largely unknown, a critical gap to unveiling the complexities of dopamine neuron function. We investigated these questions here, using fiber photometry and the dopamine biosensor dLight1.3b in the rat VTA/SNc. First, we show that dopamine release in the midbrain is dynamically modulated by local and distal factors. Optogenetic activation of VTA dopaminergic or GABAergic neurons drove an increase or decrease in VTA dopamine signaling, respectively. Further, activation of D1-neuron inputs from the nucleus accumbens drove an increase in somatodendritic dopamine signals. We next investigated VTA/SNc dopamine dynamics during appetitive conditioning, where a cue (tone) was associated with sucrose delivery, and during aversive conditioning, where a different tone was associated with footshock. Lastly, we employed dual color photometry to simultaneously monitor midbrain somatodendritic dopamine dynamics and dopamine neuron activity. During Pavlovian reward and fear conditioning, we identified characteristic, heterogeneous dopamine

signaling to sucrose reward and aversive shock across different subregions of the VTA/SNc. Conditioned, cue-evoked somatodendritic dopamine responses were not consistently apparent to the reward predictive tone even after extended training, while fear cues elicited a strong dopamine signal. In contrast, dopamine neurons themselves were strongly activated by conditioned cues after both reward and fear learning. Our results offer new insight into somatodendritic dopamine dynamics during learning and will have implications in understanding the complex regulation of midbrain dopamine neurons during motivated behavior.

Disclosures: G. Stemmler: None. A.R. Wolff: None. B.T. Saunders: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.18/V8

Topic: H.03. Motivation

Support: NIH F31 DA060004
NIH R00 DA042895
NIH R01 MH129370
NIH R01 MH129320
NIH R01 DA057292
NIH P30 DA048742

Title: Basolateral amygdala dopaminergic system tracks dynamic drug seeking behavior

Authors: *M. A. BRICKNER, W. E. SZOT, A. R. WOLFF, M. J. THOMAS, B. T. SAUNDERS;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Environmental cues can reinforce actions and evoke strong, dynamic motivational states during drug seeking and craving to prompt relapse. The basolateral amygdala (BLA) is critical for the associative learning that underlies this process, via the linking of affective valence to sensory stimuli that predict biologically relevant outcomes. Dopamine (DA) signaling is also critical for learning and cue-driven motivational states. The BLA receives dense dopaminergic projections and is enriched with D1 dopamine receptors (D1DRs). In recent work, we and others demonstrated that intermittent access to cocaine promotes a sensory gated, state-level control of motivation that results in binge-like seeking profiles thought to approximate human drug use. How BLA dopamine and D1DR activity functions in addiction remain largely unexplored. To begin, we used simultaneous in vivo optogenetic excitation of ventral tegmental area (VTA) TH+ neurons paired with fiber photometry of DA in the BLA. Optogenetic stimulation of VTA TH+ cell bodies results in proportional dopamine release dynamics in the BLA, and this dopamine transmission is modulated by cocaine - as evoked VTA to BLA dopamine transmission is significantly larger 7 days after cocaine exposure. Further, we probed whether BLA D1-neurons

promote reinforcement using intracranial self-stimulation (ICSS). Optogenetic activation of BLA D1-neurons is reinforcing, as rats will readily nose poke to receive self-stimulation. Finally, we used fiber photometry to measure in vivo dopamine signaling and D1-neuron activity in the BLA during an intermittent access self-administration (IntAc) paradigm using dLight and GCaMP, respectively, with high spatiotemporal precision. The IntAc paradigm includes periods of reward available and unavailable periods, and the shifts between the two are indicated by changes in sensory stimuli to probe whether the BLA is involved in the state-level encoding associated with reward seeking for both natural rewards and drugs of abuse. Both BLA dopamine and D1-neuron signals emerged in response to cocaine infusions as well as sucrose consumption. These signals also came to track the presence of dynamic, sensory-guided reward seeking motivational states during the transitions between drug availability periods and sucrose availability periods. Dopamine and D1-neuron signals exhibited different temporal profiles during state transitions and cues, suggesting that they may underlie unique facets of reward-related behaviors. In ongoing studies, we are exploring the functional role of D1-containing BLA neurons in state-level control of drug seeking using optogenetics.

Disclosures: M.A. Brickner: None. W.E. Szot: None. A.R. Wolff: None. M.J. Thomas: None. B.T. Saunders: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.19/V9

Topic: H.03. Motivation

Support: NIH Grant F31 DA060069
NIH Grant T32 DA007234
NIH Grant R00 DA042895
NIH Grant R01 MH129320
NIH Grant R01 MH129370
NIH Grant 5P30DA048742-04

Title: Differential representations of valence and value among local versus distal VTA GABA neuron projections

Authors: *M. STELZNER¹, A. R. WOLFF², B. T. SAUNDERS²;

²Dept. of Neurosci., ¹Univ. of Minnesota, Minneapolis, MN

Abstract: Forming associations between environmental cues and biologically relevant outcomes is vital for effective decision making. The Ventral Tegmental Area (VTA) plays a central role in associative learning and cue-driven behavior via its two main neuronal subtypes: dopamine (DA) and GABA. DA neurons are well characterized for their role in reward prediction and reinforcement. GABA neurons were long thought to represent an “anti-reward” signal because of

their ability to inhibit local DA neurons through direct synapses and their responsiveness to aversive stimuli. More recent work indicates that VTA GABA neuron signaling is also critical to reward prediction and appetitive event encoding. Collectively, these valence-independent signals suggest heterogeneity among VTA GABA neurons. In addition to making local synapses with DA neurons, GABA neurons send projections to distal regions, such as the nucleus accumbens (NAc) and ventral pallidum (VP). To investigate this diversity, we used a viral approach to bias targeting of calcium indicators to VTA GABA neurons that preferentially make local (intra-VTA) synapses, versus those which preferentially project outside of the VTA. In one group of rats (“local” group), we delivered an adeno-associated virus (AAV) with Cre expressed under the GAD1 promoter co-infused with an AAV expressing retrograde-FLP, as well as another AAV expressing GCaMP6f in a Cre-ON FLP-ON manner. This resulted in GCaMP6f expression in VTA GABA neurons that make local synapses. In a separate group (“distal” group) of rats, we delivered a similar viral cocktail but GCaMP6f expression was driven in a Cre-ON FLP-OFF manner, to target VTA GABA neurons that do not make local synapses. In Pavlovian conditioning paradigms, we then paired discrete auditory cues with sucrose reward or mild footshock while recording activity using fiber photometry. Neural activity in the local group showed increases to both appetitive and aversive outcomes, consistent with a salience-like encoding profile. In contrast, the distal group showed anatomical heterogeneity and value-like signals, where neural activity strongly encoded reward in some rats, and preferentially encoded shock in others. Given this value encoding, we also tested reinforcement of VTA GABA neurons and their striatal projection targets using optogenetics. We found that rats will robustly self-stimulate VTA GABA neuron cell bodies and will self-stimulate VTA GABA terminals in the NAc and VP to a lesser degree. Together, our results suggest that VTA GABA projections outside of the VTA have roles in valence and value encoding that are distinct from local projections.

Disclosures: M. Stelzner: None. A.R. Wolff: None. B.T. Saunders: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.20/V10

Topic: H.03. Motivation

Support: UMN MnDRIVE (Minnesota’s Discovery, Research and Innovation Economy) Initiative
R01MH129370

Title: The parafascicular thalamus encodes directed attention towards cues

Authors: *L. KUPER¹, A. R. WOLFF², B. T. SAUNDERS²;

¹Neurosci., Univ. of Minnesota, Minneapolis, MN; ²Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Cue reactivity acts as the foundation for attention, motivation and learning. Many psychiatric conditions stem from dysregulated reactivity to cues in the environment. While many studies have explored the role of striatal regions in cue reactivity, the role of thalamic circuits is relatively unexplored. The parafascicular (PF) thalamus is well-placed as an integrative hub for cue processing. It receives direct inputs from the substantia nigra as well as the superior colliculus, an area involved in guiding attention to unexpected stimuli, and is known to be activated during behaviorally significant sensory events. The PF sends dense excitatory outputs throughout the striatum, and is a main input and modulator of striatal cholinergic interneurons. Limited studies on PF have revealed that it plays an important role in behavioral flexibility, but little is known about how in vivo PF activity tracks learning and behavior. To investigate this, I recorded PF neuronal calcium activity using fiber photometry during a series of cue-directed conditioning tasks. In a Pavlovian conditioned approach task, where a discrete, approachable lever cue predicted sucrose reward, the PF developed strong sustained responses during cue presentations, which scaled with learning. Integration of behavioral trajectory data from DeepLabCut revealed that the PF signals track individual patterns of cue-directed orientation and approach. These data suggest that the PF encodes attentional shifts towards salient stimuli. In additional studies, optogenetic activation of the PF resulted in head orientation and directed turning motion, further suggesting that PF neurons are important for steering behavior. However, optogenetic experiments also revealed that rats have moderate preference for self-stimulating the PF, suggesting that it also has reward-related outputs. This was supported in the recording data, where we saw an increase in PF activity during reward consumption, while the rats were otherwise immobile. In ongoing studies, I am investigating the hypothesis that the PF multiplexes signals for salience/value and directed approach via differential activity of projections to striatal subregions, including the nucleus accumbens and dorsomedial striatum.

Disclosures: L. Kuper: None. A.R. Wolff: None. B.T. Saunders: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.21/V11

Topic: H.03. Motivation

Support: NINDS Grant T32-NS105604
MSTP Grant 5T32-GM008244-37
NIMH Grant R01MH129370

Title: The superior colliculus exhibits distinct neuronal and dopaminergic dynamics in Pavlovian conditioning

Authors: *I. K. GREEN¹, C. L. POISSON³, A. R. WOLFF², B. T. SAUNDERS²;
¹Neurosci., ²Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN; ³Univ. of Minnesota Grad. Program In Neurosci., Minneapolis, MN

Abstract: Alterations in attentional processes and salience encoding underlie the pathophysiology of many neuropsychiatric disorders, ranging from attention-deficit/hyperactivity disorder (ADHD) to substance use disorders (SUDs). Sorting out the mechanisms underlying how sensory information is consolidated and transmitted to mediate these processes is critical in expanding treatment modalities for diseases in which attentional processing is affected. Recent work has positioned the superior colliculus (SC) as a compelling candidate for integrating sensory information to mediate attention and cue-evoked behavior. However, the neural circuitry forming the basis for these functions is relatively unexplored. To address this gap, we first investigated the role of SC neurons in a Pavlovian cue-reward learning task using in vivo fiber photometry to record calcium signaling from deep layers of the SC utilizing GCaMP8f, a fluorescent calcium indicator. Our findings show robust SC neuronal responsivity to visual cues predicting sucrose. We then examined calcium signaling when visual cues predicted either neutral tap water delivery or an aversive shock and found that the SC signal magnitude tracked cue salience. Further, SC signal magnitude was positively correlated with speed and orientation to cues, suggesting that the SC may drive movement invigoration toward salient stimuli. In addition to sensorimotor inputs, the SC receives non-canonical dopaminergic input and also contains anatomically segregated dopamine receptors, raising the potential for behaviorally relevant dopamine signaling in the SC. To explore this, we used dLight1.3b, a fluorescent dopamine biosensor, to record dopamine dynamics in the same Pavlovian conditioning paradigms as above. These results, in contrast to the SC neuronal signals, suggest that dopamine signaling in deep layer SC decreases in response to visual cues and negatively correlates with movement vigor. Future directions include further characterization of neuronal subpopulations in attention and addiction-related behavioral paradigms to evaluate how this region may be implicated in disorders of attention and salience encoding.

Disclosures: I.K. Green: None. C.L. Poisson: None. A.R. Wolff: None. B.T. Saunders: None.

Poster

PSTR034: Neural Circuits of Reward-Related Behavior

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR034.22/W1

Topic: H.03. Motivation

Title: Coadministration antagonist dopamine receptor D4 with CB2 receptor agonist decreases binge-like intake of palatable food in mice

Authors: *L. RODRIGUEZ-SERRANO¹, M. CHAVEZ HERNANDEZ²;

¹Facultad de Psicología, Univ. Anáhuac México, Estado de México., Mexico; ²Facultad Psicología, Univ. Anáhuac, Mexico, Mexico

Abstract: Introduction: Food intake is regulated by two systems: homeostatic and hedonic. An imbalance between these systems can induce overconsumption, such as binge eating disorder (BED), and is associated with dysregulation of the dopamine reward system. The cannabinoid

type 2 receptor (CB2R) has been identified in dopamine neurons and may play an important role in motivated behaviors, including food intake. Nevertheless, the interaction between the dopamine D4 (DRD4) receptor and CB2R in binge-like intake has not yet been identified. Therefore, the present study aims to evaluate the effects of intraperitoneal administration of DRD4 antagonist (L-745870), as well as the coadministration of DRD4 antagonist with either CB2R agonist (HU308) or antagonist (AM630), on binge-like intake of palatable food (PF) in adult male mice. Methods: We used adult male 34 C57BL6/J mice. All animals were housed individually and had *ad libitum* access to standard diet (SD) and water. To evaluate binge-like intake, the animals had 1 h of access to PF during 12 baseline binge eating test (BET) sessions. Mice were then randomly assigned to the following treatment groups: 1) vehicle; 2) L-745870; 3) L-745870-HU308, 4) L-745870+AM630 to be evaluated under the effect of treatments for three additionally BET sessions. Results: Our results show that DRD4 antagonist reduced binge-like intake of PF, and that a coadministration with a CB2R agonist induced an even more pronounced reduction of binge-like intake. Conclusion: These findings suggest an interaction between the dopaminergic and endocannabinoid systems in the modulation of binge-like intake of PF in adult mice, where CB2R activation participates in modulating reward pathways and reducing binge-like behavior.

Disclosures: L. Rodriguez-Serrano: None. M. Chavez Hernandez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.01/W2

Topic: H.02. Reward and Appetitive Learning and Memory

Title: The effects of torpor on associative memory in big brown bats

Authors: *J. M. COLE¹, C. F. MOSS¹, N. FINGER², D. DRIESKENS³, M. JAROSZEWSKI², M. RHO¹, N. HWANG¹;

¹Dept. of Psychological and Brain Sci., ²Johns Hopkins Univ., Baltimore, MD; ³department of psychological and brain sciences, Federal Univ. of Rio Grande do Norte, João Pessoa, Brazil

Abstract: Big brown bats (*Eptesicus fuscus*) undergo seasonal torpor from October to February, during which they reduce food and water intake and experience a ~15°C drop in body temperature. Despite this prolonged physiological downregulation, they rapidly resume normal activity in the spring. Little is known about how associative memories, which are critical for foraging and social interaction, are retained across this period of metabolic suppression. To investigate this, four bats were trained on a maze task involving the identification of an auditory and visual cue to receive a reward. After reaching a predefined success threshold across trials, the bats were divided into torpor and non-torpor groups. The bats in the torpor condition were housed in a 7°C environment while the non-torpor bats were in a 24°C environment. The bats remained under these conditions for three months before being retested on the original task.

Behavioral performance was recorded and analyzed using DeepLabCut. Bats in the torpor group exhibited no significant decline in task performance, suggesting retention of the learned association. The non-torpor group produced inconclusive results. Although preliminary, these findings suggest that torpor may play a role in memory preservation. This study provides initial evidence that associative memory can persist through extended torpor. If confirmed with larger sample sizes, these results could inform future investigations into the neurobiological mechanisms enabling memory stability during extreme physiological states.

Disclosures: J.M. Cole: None. C.F. Moss: None. N. Finger: None. D. Drieskens: None. M. Jaroszewski: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.02/W3

Topic: H.01. Fear and Aversive Learning and Memory

Support: Ludwig Family Foundation
NIH Early Independence Award (DP5 OD023106-01)
NIH Transformative R01 Award
Young Investigator Grant from the Brain and Behavior Research Foundation
McKnight Foundation Memory and Cognitive Disorders award
Pew Scholars Program in the Biomedical Sciences
Air Force Office of Scientific Research (FA9550-21-1-0310)

Title: Prefrontal and hippocampal astrocytic and neuronal dynamics across fear learning and retrieval

Authors: *M. BUZHARSKY¹, R. SUTHARD², R. A. SENNE³, A. PYO⁴, S. RAMIREZ³;
¹Boston Univ. Grad. Program In Neurosci., Boston, MA; ²Grad. Program for Neurosci., Boston Univ. Grad. Program For Neurosci., Boston, MA; ⁴Psychological & Brain Sci., ³Boston Univ., Boston, MA

Abstract: Both the ventral hippocampal CA1 (vCA1) and medial prefrontal cortex (mPFC) are critical for the acquisition and maintenance of fear memories. Our recent findings suggest that these regions exhibit task-specific and affective state-dependent synchrony, underscoring their coordination during memory processes. While much attention has been given to the neuronal circuitry underlying fear memory, much less is known about the contribution of non-neuronal cell types, particularly astrocytes. Astrocytes are emerging as key modulators of neuronal activity, capable of regulating network synchrony and coordinating functionally-relevant neuronal populations. To investigate the real-time dynamics of both astrocytes and neurons in fear memory processing, we employed fiber photometry to simultaneously record activity in the

mPFC and vCA1. Specifically, we used cell-type-specific expressions of genetically encoded calcium indicators, neuronal jRGECO1a and astrocytic GCaMP6f, in both brain regions. Mice were subjected to a contextual fear conditioning (CFC) paradigm, including the phases of learning, recent memory recall, and remote memory recall (i.e. 2 weeks post-conditioning). Our findings are twofold: first, we observe robust time-locking of neurons and astrocytes in both brain regions to foot shocks, as well as increased cross-regional cross-correlation of vCA1 astrocytes to mPFC astrocytes. Secondly, astrocytes and neurons display stereotyped calcium transients aligned to freezing onsets. Our ongoing experiments investigate how chemogenetically perturbing astrocytes alters neuronal and astrocytic calcium signaling in upstream mPFC. To that end, we inject vCA1 astrocytes with hM4D(Gi) and administer deschloroclozapine (DCZ) ligand during fear conditioning while recording upstream mPFC neurons and astrocytes using fiber photometry in the same CFC paradigm. This work will inform how prefrontal and hippocampal astrocytes and neurons change their dynamics to drive fear acquisition and retrieval, and how perturbing hippocampal astrocytes affects distal cellular dynamics and behavior.

Disclosures: **M. Buzharsky:** None. **R. Suthard:** None. **R.A. Senne:** None. **A. Pyo:** None. **S. Ramirez:** None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.03/W4

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH R01MH051399
Hope for Depression Research Foundation

Title: Psychedelic Rescue of Sex-Specific Serotonin Circuits in Approach-Avoidance Conflict

Authors: ***G. ROJAS**¹, G. DI SALVO⁴, T. MARKOVIC⁵, A. M. MINIER-TORIBIO², V. KONDEV¹, L. HOLT⁶, C. BLASCHKE³, A. GODINO³, F. J. MARTINEZ-RIVERA⁷, E. J. NESTLER⁸;

²Nash Family Dept. of Neurosci., ¹Icahn Sch. of Med. at Mount Sinai, New York, NY; ³Icahn Sch. of Med. at Mount Sinai, New York, NY; ⁴Neurosci., Icahn Sch. of Med. At MSSM Mount Sinai Grad. Training Program In Neurosci., New York, NY; ⁵Neurosci., Icahn Sch. of Med., New York, NY; ⁶Neurosci. Dept., Mount Sinai Sch. of Med., New York, NY; ⁷Neurosci., Univ. of Florida, Gainesville, FL; ⁸Icahn Sch. of Med. At Mount Sinai, New York, NY.

Abstract: Approach-avoidance (A-A) strategies exemplify sex-dependent biases necessary for adaptive behavior, relying on emotional regulation, learning and memory, and cognitive processing to generate appropriate responses. Notably, females face a higher lifetime risk of developing anxiety- and fear-related disorders, often exhibiting deficits in extinguishing traumatic memories, characterized by a decline in approach behavior toward rewards in favor of

avoiding perceived threats. Despite these deleterious effects on females featuring heightened decision-making impairments with unclear neurobiological mechanisms, the incorporation of female subjects with sex as a biological variable (SABV) in research studies remains a challenge. Previous studies highlight the role of serotonergic (5HTergic) neurotransmission in the medial prefrontal cortex (mPFC) in processing reward vs. threat scenarios, with 5HT_{2A} receptors (5HT_{2ARs}) signaling associative learning and potentially displaying sex differences in binding affinity. For instance, serotonergic modulators, including psychedelic substances, appear to exhibit promising results in alleviating symptoms of stress-associated disorders (e.g., depression and PTSD) involving poor decision-making control under conflict situations with sex-dependent divergence. Here, we use the platform-mediated avoidance (PMA) task in mice to model and assess the translational effects of combining extinction-based “therapy” with psychedelic exposure (e.g., LSD) in restoring a balanced decision-making process under A-A conflict. We complement these behavioral characterizations with in vivo fiber photometry to record fluorescent signals as a proxy for prefrontal 5HT neurotransmission (5HT release), and single-cell transcriptomics to identify the specific cell types that may contribute to sex-dependent differences in circuit function and response to psychedelics. Together, these approaches allow us to delve deeper into the neurobiology of A-A behaviors guided by serotonergic plasticity and reveal mechanisms by which psychedelics may exert health-promoting effects in psychiatric conditions that disproportionately affect females.

Disclosures: G. Rojas: None. G. Di Salvo: None. T. Markovic: None. A.M. Minier-Toribio: None. V. Kondev: None. L. Holt: None. F.J. Martinez-Rivera: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.04/W5

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Transformative Award
Ludwig Family Foundation
FA9550-21-1-0310
Pew Scholars Program in the Biomedical Sciences
Chan-Zuckerberg Initiative
Center for Systems Neuroscience distinguished fellowship

Title: Psychedelics Relax Priors and Reshape Orbitofrontal Dynamics

Authors: *C. DELGADO SALLEN¹, S. AHMED², A. KHAWAJA-LOPEZ², B. LEE², R. A. SENNE², B. B. SCOTT³, S. RAMIREZ²;

¹Psychological and Brain Sci., ³Psychological & Brain Sci., ²Boston Univ., Boston, MA

Abstract: Psychedelics such as psilocybin and ketamine are gaining attention as rapid-acting treatments for psychiatric disorders, yet the mechanisms by which they alter cognition remain unclear. A key hypothesis—the REBUS model—proposes that psychedelics relax high-level priors, allowing bottom-up sensory information to exert greater influence over perception and behavior. Here, we test this model in mice performing a free-response perceptual decision-making task that disambiguates prior-driven and sensory-driven decision strategies. Acute administration of psilocybin or ketamine significantly slowed decision times and improved accuracy. Behavioral modeling that combined drift diffusion and GLM-HMM frameworks revealed that these changes were mediated by increased decision thresholds and a marked shift into sensory-engaged cognitive states. Whole-brain c-Fos mapping identified a distributed decision-making network, with psychedelics selectively modulating cortical and subcortical nodes. Calcium imaging in the orbitofrontal cortex (OFC)—a key region for integrating priors and sensory inputs—revealed preserved decision-related selectivity under psychedelics, while exhibiting reduced neuronal correlations—population-level signatures of weakened top-down influence and relaxed priors. Together, these results provide circuit-level support for the REBUS model, showing that psychedelics reconfigure brain-wide and local dynamics to promote more deliberate, flexible, and sensory-driven decision policies.

Disclosures: C. Delgado Sallent: None. S. Ahmed: None. A. Khawaja-Lopez: None. B. Lee: None. R.A. Senne: None. B.B. Scott: None. S. Ramirez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.05/W6

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Transformative Award
Ludwig Family Foundation
Air Force Office of Scientific Research award (FA9550-21-1-0310)
Pew Scholars Program in the Biomedical Sciences
Chan-Zuckerberg Initiative
Howard Hughes Medical Institute Gilliam Fellowship

Title: Orbitofrontal cortex network dynamics across reward and avoidance learning

Authors: *A. J. CABAN¹, C. DELGADO SALLENT², S. PARK¹, S. RAMIREZ¹;

²Dept. of Psychological and Brain Sci., ¹Boston Univ., Boston, MA

Abstract: Learning to accurately and flexibly distinguish threatening from rewarding contexts is critical in our daily lives. However, how prior knowledge is organized in a manner that supports flexible retrieval of distinct memories to allow adaptive behavior is not well understood. The orbitofrontal cortex (OFC) is thought to contain knowledge structures based on multiple prior

experiences, which can be deployed to aid flexible behavioral decisions in the future, though how these knowledge structures are formed and organized remains unknown. Here, we leveraged single-cell calcium imaging of OFC ensembles as animals learn two cue-driven behaviors, i.e. reward-seeking and threat-avoidance, within the same context. Briefly, mice learn a 30s tone-cue co-terminates with a shock they can avoid by stepping on a platform, while a 30s light-cue signals reward availability for which they can poke at a nearby nose port. Across five days, animals learn to avoid- and reward-seek accordingly. We observe that at the population level, OFC ensembles progressively represent same-valance cue-behavior pairs similarly while orthogonalizing dissimilar cue-behavior pairs. Moreover, by a leveraging graph- theoretical approach we uncover that at a network level, reward-seeking and avoidance associations develop diverging properties. Specifically, and across learning, OFC networks become more rigid and localized during reward-seeking while becoming more flexible and segregated during threat avoidance. Our ongoing work seeks to uncover properties at the single cell lever that predict the role of a cell in the network across learning. Together our data, looks to uncover principles by which distinct memories are stored and recalled to enable flexible behavior.

Disclosures: A.J. Caban: None. C. Delgado Sallent: None. S. Park: None. S. Ramirez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.06/W7

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Transformative Award
Ludwig Family Foundation
Air Force Office of Scientific Research award (FA9550-21-1-0310)
Pew Scholars Program in the Biomedical Sciences
Chan-Zuckerberg Initiative
Neurophotonics Center at Boston University
Center for Systems Neuroscience, Boston University

Title: A hippocampal astrocytic sequence emerges during learning and memory

Authors: *R. SUTHARD¹, R. A. SENNE², R. CAO⁵, S. J. COELLO³, A. H. MONASTERIO⁶, E. A. RUESCH⁷, M. D. BUZHARSKY⁴, M. W. HOWARD³, S. RAMIREZ³;

¹Psychological & Brain Sci., ²Grad. Program for Neurosci., ³Dept. of Psychological and Brain Sci., ⁴Grad. Program In Neurosci., Boston Univ., Boston, MA; ⁵Dept. of Psychological and Brain Sci., Univ. of Tennessee, Knoxville, TN; ⁶Psychological and Brain Sci., Univ. of Utah, Boston, UT; ⁷Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: To create episodic memories with high granularity, the hippocampus must encode information by indexing the spatial and temporal aspects of an experience. Within the

hippocampus, pyramidal cells function as place and time cells, developing spatially-tuned receptive fields within an environment or tiling the temporal plane through sequential activity. Glial cells, on the other hand, have been largely ignored in this realm of spatiotemporal processing until recently. Recent findings have shown that astrocytes interface with neurons in a synergistic and complementary manner to represent spatial information in dorsal CA1 of the hippocampus (dCA1) and may encode reward location via similar spatial mechanisms. Further, computational modeling has proposed that astrocytic neuromodulation is sufficient to generate neuronal place fields via enhanced theta oscillations and plasticity changes. Together, these findings open the door to studying astrocytic involvement in spatiotemporal processing during memory formation and retrieval and how it relates to neuronal activity within these circuits. To investigate the role of astrocytes in spatiotemporal processing within the hippocampus during memory encoding and recall, we employed one-photon imaging in the dCA1 region. To accomplish this, we injected AAV-GfaABC1D-GCaMP6f into the pyramidal cell layer of the hippocampus of both male and female C57BL/6J mice to selectively express the genetically-encoded calcium indicator in astrocytes. We paired this with implantation of a gradient-index lens to record freely-moving activity across a standard contextual fear conditioning paradigm. To our knowledge, this is the first time a study has successfully performed longitudinal registration of astrocytic cell population using 1p calcium imaging, thus permitting the tracking of a stable population of these cells in freely-moving mice. In response to foot shock, astrocytes generated robust calcium-event sequences with a time-compressed structure akin to canonical hippocampal time cells. Upon reexposure to the conditioned context, these astrocytic sequences persisted in the absence of shock, maintaining their time-compressed structure. Moreover, astrocytes active on the previous day retained a preserved sequential structure and showed an inverse relationship with freezing behavior, indicating memory-specific properties. This phenomenon was not observed in a context different from the initial fear conditioning chamber. Taken together, these findings suggest a role for astrocytes in temporal coding within hippocampal circuits and may serve as a behaviorally relevant memory retrieval mechanism.

Disclosures: R. Suthard: None. R.A. Senne: None. R. Cao: None. S.J. Coello: None. A.H. Monasterio: None. E.A. Ruesch: None. M.D. Buzharsky: None. M.W. Howard: None. S. Ramirez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.07/W8

Topic: H.02. Reward and Appetitive Learning and Memory

Support: JSPS KAKENHI Grant Number 22K07332

Title: Differential roles of locus coeruleus and ventral tegmental dopamine inputs to the dorsal hippocampus in sucrose-conditioned place preference

Authors: *N. KAI¹, Y. SAITOH², C. KAMIYOSHIHARA³, M. ISHIKAWA³, N. OHKAWA⁴; ²Lab. for Memory and Cognitive Function, Res. Ctr. for Advanced Med. Sci., ¹Dokkyo Med. Univ., Mibu Machi, Shimotsuga-Gun, Tochigi, Japan; ³Lab. for Memory and Cognitive Function, Res. Ctr. for Advanced Med. Sci., Dokkyo Med. Univ., Mibu-machi, Shimotsuga-gun, Tochigi, Japan; ⁴Lab. for Memory and Cognitive Function, Res. Ctr. for Advanced Med. Sci., Dokkyo Med. Univ., Mibu Machi, Shimotsuga-Gun, Japan

Abstract: The formation and retrieval of episodic memory associated with positive emotions are essential for survival in animals, aiding in efficient foraging. In mammals, such adaptive behaviors depend on spatial memory representations encoded by pyramidal cell assemblies in the dorsal hippocampus. Dopamine (DA) modulates plasticity, synaptic transmission, and network activity in hippocampal circuits crucial for this type of memory. However, the specific source of hippocampal dopamine involved in episodic memory formation remains unclear, as it may originate from either the ventral tegmental area (VTA) or the locus coeruleus (LC). We examined the roles of these dopaminergic inputs in positive affective memory using a single-trial conditioned place preference (CPP) paradigm in mice. In this task, mice learned to associate one compartment of a two-chamber apparatus with a reward (sucrose or condensed milk) and the other with water. On the test day, mice showed a preference for the reward-associated compartment, indicating successful memory acquisition. Bilateral infusion of the D1-class DA receptor antagonist SCH-23390 into the dorsal CA1 region during training impaired the acquisition of sucrose CPP but not condensed milk CPP. Furthermore, chemogenetic inactivation of tyrosine hydroxylase (TH)-expressing neurons in the LC disrupted sucrose CPP, whereas inactivation of VTA dopaminergic neurons had no effect. Importantly, LC inhibition did not affect sucrose consumption or exploration during training, suggesting a specific role in memory formation rather than motivation or locomotion. These findings indicate that dopaminergic inputs from the LC to the dorsal hippocampus are necessary for acquiring sucrose-associated memory in a single-trial learning context, while inputs from the VTA are not essential. The role of the LC-DA system in supporting hippocampal dynamics related to persistent memory for palatable experiences will be further discussed.

Disclosures: N. Kai: None. Y. Saitoh: None. C. Kamiyoshihara: None. M. Ishikawa: None. N. Ohkawa: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.08/W9

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Transformative Award
Ludwig Family Foundation
Air Force Office of Scientific Research award (FA9550-21-1-0310)
Pew Scholars Program in the Biomedical Sciences

Chan-Zuckerberg Initiative
Neurophotonics Center at Boston University
Center for Systems Neuroscience

Title: Aging alters neuronal-astrocyte dynamics across various behavioral states.

Authors: *H. LEBLANC^{1,3}, M. BUZHARSKY⁴, S. RAMIREZ²;

²Psychological and Brain Sci., ¹Boston Univ., Boston, MA; ³Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA; ⁴Boston Univ. Grad. Program In Neurosci., Boston, MA

Abstract: Aging is associated with widespread changes in brain structure and function, including synaptic loss, reduced neurogenesis, impaired blood-brain barrier integrity, and chronic low-grade neuroinflammation. These alterations can disrupt glial-neuronal communication, contributing to diminished behavioral flexibility and cognitive decline. Astrocytes perform diverse and essential roles in the central nervous system, including vascular regulation, immune surveillance, metabolic support, and modulation of synaptic activity via the tripartite synapse. Notably, aging induces transcriptomic and functional changes in astrocytes that may compromise these roles and contribute to broader neural dysfunction. However, how these age-related shifts affect real-time astrocyte-neuron dynamics, particularly in behaviorally relevant contexts, remains poorly understood. To address this, we performed dual-color fiber photometry in the medial prefrontal cortex (mPFC) and ventral hippocampus (vHPC)—regions especially vulnerable to aging—in young and aged mice. Animals were exposed to a spectrum of behavioral paradigms, ranging from highly aversive (repeated foot shocks) to moderately stressful (tail suspension, elevated zero maze) to minimally stressful (spontaneous home cage behavior). Across tasks and brain regions, we observed age-associated differences in calcium activity within both astrocytes and neurons. While both cell types remained responsive across conditions, alterations varied by behavioral context. In general, aging was associated with larger-amplitude but delayed astrocyte signaling and disrupted neuron-astrocyte coupling. This shift may reflect heightened intrinsic excitability of intracellular calcium release pathways—potentially driven by age-related oxidative stress and morphological features that sensitize astrocytic processes to calcium flux—and suggests altered temporal coordination between astrocytes and neurons during behaviorally relevant states. Ongoing work using high-resolution behavioral tracking aims to map these physiological dynamics onto discrete behavioral features. Together, these results provide a foundation for understanding how normal aging reshapes glial-neuronal interactions and may inform future studies of vulnerability to neurodegenerative and other age-related brain disorders.

Disclosures: H. Leblanc: None. M. Buzharsky: None. S. Ramirez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.09/W10

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Transformative Award
Ludwig Family Foundation
Air Force Office of Scientific Research award (FA9550-21-1-0310)
Pew Scholars Program in the Biomedical Sciences
Chan-Zuckerberg Initiative
Neurophotonics Center at Boston University and the Center for Systems Neuroscience

Title: Memory Stability and Representational Drift in Hippocampal Engram Cells

Authors: *A. ITO¹, A. MONASTERIO⁴, S. COELLO², A. TADIGADAPA², J. F. NORMAN², J. A. WHITE³, S. RAMIREZ²;

¹Grad. Program for Neurosci., ³Biomed. Engin., ²Boston Univ., Boston, MA; ⁴Univ. of Utah, Salt Lake City, UT

Abstract: The stability of memory traces over time is critical for adaptive behavior. However, neural representations in the hippocampus change even in the absence of new learning, a phenomenon termed representational drift. This presents a fundamental question in neuroscience: how can memories remain stable if the ensembles encoding them are dynamic? While drift has been recently well documented, its functional implications remain a mystery. Specifically, it is unclear whether all neurons equally undergo drift, or whether memory-encoding engram cells exhibit enhanced stability to support persistent memory.

Here, we test the hypothesis that engram cells are more stable over time than non-engram cells and that this stability may underlie long-term memory retention. We used longitudinal in vivo two-photon calcium imaging to track hippocampal CA1 activity across days in awake, head-fixed mice following contextual fear conditioning. Activity-dependent genetic labeling enabled us to identify engram cells within the broader population of cells. This design allowed direct comparison of cellular dynamics between engram and non-engram cells within the same local hippocampal circuit.

Our preliminary analyses reveal that, at the population level, engram and non-engram cells display comparable mean activity rates and pairwise correlations across days. Accordingly, we propose that these aggregate measures may mask functional heterogeneity within each population. Our ongoing analyses include dimensionality reduction and ensemble decoding to isolate stable versus labile subpopulations and assess their predictive value for memory recall. We predict that a subset of engram cells will form a temporally stable “core” whose structure is preserved across days and whose activity correlates with behavioral expression of memory. Moreover, we are investigating how natural memory retrieval—exposing an animal to the same reward-associated context—influences drift. In these experiments, we predict that engram cells will exhibit greater representational stability and reduced drift, compared to non-engram cells. This work aims to reveal how memory systems preserve stable behavioral recall despite dynamic neural representations, highlighting coding strategies that balance plasticity and persistence.

Disclosures: A. Ito: None. A. Monasterio: None. S. Coello: None. A. Tadigadapa: None. J.F. Norman: None. J.A. White: None. S. Ramirez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.10/W11

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Transformative Award
The Ludwig Family Foundation
The Air Force Office of Scientific Research award (FA9550-21-1-0310)
The Pew Scholars Program in the Biomedical Sciences
The Chan-Zuckerberg Initiative
Neurophotonics Center at Boston University and the Center for Systems Neuroscience

Title: Two-photon imaging of hippocampal neurons and astrocytes in awake behaving mice

Authors: *S. J. COELLO¹, R. L. SUTHARD², R. A. SENNE¹, M. BUZHARSKY⁴, A. TADIGADAPA³, A. MONASTERIO⁵, S. RAMIREZ¹;
²Psychological and Brain Sci., ¹Boston Univ., Boston, MA; ³Boston Univ., Sharon, MA; ⁴Boston Univ. Grad. Program In Neurosci., Boston, MA; ⁵Psychological and Brain Sci., Univ. of Utah, Boston, UT

Abstract: Compelling evidence from both experimental data and computational models indicate that astrocytes are integral to memory-related mechanisms. Recent work from our lab used one-photon calcium imaging in freely-moving mice and found that hippocampal CA1 astrocytes exhibit robust, time-compressed calcium activity sequences during contextual fear conditioning and recall, akin to hippocampal time cells. However, these prior results did not measure whether or not neurons were cooperatively active with astrocytes to support memory functions. To address this gap, we performed dual-color two-photon calcium-imaging in head-fixed male C57BL/6J mice to simultaneously monitor astrocytic and neuronal activity in dorsal CA1 across fear learning and recall. To differentially label each population, we co-injected AAV9-hSyn-jRGECO1 and AAV5-GfaABC1D-cyto-GCaMP6f into the pyramidal cell layer of dCA1. This approach enabled real-time monitoring of both cell types as mice voluntarily locomoted on a treadmill. Here, we provide proof-of-concept data by quantifying the temporal coordination between astrocytic and neuronal activity, and our current work aims to determine whether these populations engage in structured, sequence-like dynamics across fear learning and recall. Our preliminary data reveal tightly coordinated activity between astrocytes and neurons during locomotion. Moreover, our ongoing analyses will explore how these interactions evolve across learning and memory, with a particular focus on the organization and interplay of sequence-like activity patterns in both cell types. We hypothesize that fear learning will induce temporally organized astrocytic activity that aligns with neuronal sequences, reflecting a coordinated, experience-dependent dynamic between the two cell types. Such interactions may serve as a substrate for the temporal structuring and consolidation of memory traces. This work provides key methodological and mechanistic insights by implementing two-photon imaging of neurons

and astrocytes, thus allowing for high-resolution acquisition and analysis of their interactions during memory formation.

Disclosures: S.J. Coello: None. R.L. Suthard: None. R.A. Senne: None. M. Buzharsky: None. A. Tadigadapa: None. A. Monasterio: None. S. Ramirez: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.11/W12

Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Research Foundation of Korea Grant
National Research Foundation of Korea Grant RS-2024-00350621
National Research Foundation of Korea Grant RS-2019- NR040055

Title: Astrocytes amplify cortical dopamine to encode winning memory

Authors: *K. NOH^{1,3}, W.-H. CHO⁶, Y.-J. KIM², M. HWANG⁴, J.-H. BAIK⁷, S.-Y. CHOI⁸, S. LEE⁵;

²Dept. of Pharmacol., ¹Ajou Univ. Sch. of Med., Suwon, Korea, Republic of; ⁴Dept. of Brain and Cognitive Sci., ⁵Neurosci., ³Seoul Natl. Univ., Seoul, Korea, Republic of; ⁶Inst. for Neurolog. Therapeut. Rutgers-Robert Wood Johnson Med. Sch., New Jersey, NJ; ⁷Korea Univ., Seoul-City, Korea, Republic of; ⁸Physiol., Seoul Natl. Univ. Sch. of Dent., Seoul, Korea, Republic of

Abstract: Memories of winning experiences reinforce dominance hierarchies, yet mechanisms encoding these long-lasting “winning memories” remain unclear. Here, we introduce a combined Tube & Conditioned Place Preference (CPP) paradigm and applied fiber photometry, genetic manipulations, and optogenetics to characterize social competition between adult male mice. We found that initial victories trigger dopamine D2 receptor-mediated calcium activities of astrocytes in the medial prefrontal cortex (mPFC) and subsequent glutamate release. This mechanism enhances dopaminergic responses in mPFC neurons projecting to the nucleus accumbens (NAc), thereby consolidating winning memories. Upon ablation of D2 receptors in mPFC astrocytes, this effect is abolished, hindering generation of new dominance memories and a stable social hierarchy. Our findings reveal an astrocyte-driven mechanism by which mesocortical dopamine signaling reinforces victory-related neural plasticity, and provide broad insights into the cellular basis of social dominance and its underpinnings in motivational and affective disorders.

Disclosures: K. Noh: None. W. Cho: None. Y. Kim: None. M. Hwang: None. J. Baik: None. S. Choi: None. S. Lee: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.12/W13

Topic: H.01. Fear and Aversive Learning and Memory

Title: Dopaminergic prediction error signaling in *Drosophila*

Authors: *W. CHOI¹, D. GROVER²;

¹Kavli Inst. for Brain and Mind, Univ. of California, San Diego, San Diego, CA; ²Kavli Inst. for Brain and Mind, UCSD, La Jolla, CA

Abstract: Learning from experience requires detecting mismatches between what is expected and what actually occurs, and in order to learn, the brain continuously makes predictions and updates them based on sensory input. In mammals, this predictive process is thought to be guided by dopamine signals encoding both positive and negative prediction errors (PE). Midbrain dopamine neurons (DA) in mammals encode these PE signals to maximize available rewards and minimize potential dangers. DA neurons react to more reward than predicted, stay at baseline when reward is fully predicted, and exhibit reduced responses to less reward than predicted (Schultz, 2016). Despite extensive mapping of valence-specific dopamine circuits in *Drosophila melanogaster*, direct evidence for prediction error computation, has been lacking. Here, in the fly, we identified that dopaminergic neurons projecting to the central complex, in particular the ellipsoid body substructure, exhibited neural dynamics consistent with a PE-like activity during associative learning in two key ways. First, these neurons initially showed phasic calcium responses to an unexpected aversive stimulus (heat punishment) but reduced their activity as the punishment became anticipated over successive training trials. Second, DA activity shifted to the presentation of the conditioned stimulus. These PE-like responses appear after only 7-10 training trials, striking given that rodents and primates go through days and weeks of training before PE signals are seen. Consequently, the entire dopamine-modulated PE signal development can be studied in our fly paradigm, unlike mammalian studies that only examine responses before and after training. We will present findings during the intermediate learning stages of PE development, wherein these neurons show residual activity at the expected timing of punishment even when the stimulus is omitted. Our findings suggest that this pattern aligns with the temporal difference (TD) learning model, in which the prediction error reflects not only the outcome itself but also the evolving value of future states. In sum, these results provide the first glimpse of PE-like encoding in *Drosophila* DA neurons and support a conserved computational motif for associative learning across phylogeny.

Disclosures: W. Choi: None. D. Grover: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.13/Web Only

Topic: H.02. Reward and Appetitive Learning and Memory

Title: The Amplitude of the P300 ERP recorded from rat brains is a function of the information carried in predictive stimuli.

Authors: ***W. D. KLIPEC**, M. SWAN, J. KNUTH, S. LOWE, O. COREY, N. WILL, E. WIPFLER;
Psychology and Neurosci., Drake Univ., Des Moines, IA

Abstract: The P300 event Related Potential (ERP) is derived from EEG recordings as a time-locked average response to a stimulus. It occurs in humans and animals during ongoing behavior directed by a response to specific stimuli and is thought to be related to underlying cognitive processing. Previous research in our laboratory has suggested that it is a correlate of the brain's response to recognizing a conditioned reinforcing stimulus. Here, we manipulated the predictability of sucrose tablets as reinforcers for lever pressing while recording EEG during daily performance. One tone cued reaching the criterion for the reinforcement delivery (RT) while a second totally random non-target tone (NT) served as a control for brain activity following a non-informative stimulus. We manipulated the information carried in the RT by alternating fixed ratio (FR) reinforcement schedule with a series of variable ratio (VR) schedules of reinforcement. With both schedules, the RT carried the information to collect the reinforcer. We found that the peak ERP amplitude to the RT was significantly greater in the VR schedules than the FR schedules. During FR schedules, rats will anticipate reinforcer delivery and move to collect the reinforcer after making the fixed number of responses, without needing external cue. During the VR schedules the rat must rely on the RT cue to collect the reinforcer. This outcome suggests that during FR schedules the RT is redundant information. Following VR training, the additional information carried in the RT is reflected in the enhanced ERP to the RT. Accordingly, we conclude the ERP is not simply a response to a conditioned reinforcing stimulus, but also a response to the informational properties of the stimulus.

Disclosures: **W.D. Klipec:** None. **M. Swan:** None. **J. Knuth:** None. **S. Lowe:** None. **O. Corey:** None. **N. Will:** None. **E. Wipfler:** None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.14/W14

Topic: H.02. Reward and Appetitive Learning and Memory

Support: CRCNS 2113179
NeuroNex 1559632

Title: Focusing attention toward food-related odors in the honey bee, *Apis mellifera*: A comparison of methods

Authors: *K. D. DIXON¹, B. H. SMITH²;

¹Sch. of Life Sci., ²Schl Life Sci., Arizona State Univ., Tempe, AZ

Abstract: Latent Inhibition (LI) is a form of learning in which a neutral stimulus, to which animals show little response prior to conditioning, is presented over a series of trials without any consequence (reinforcement). It is an important way of focussing attention toward potentially meaningful stimuli. Later conditioning of this now 'familiar' stimulus is slowed, possibly because of reduced attention to that stimulus. Latent Inhibition has been widely studied in vertebrates and has recently been identified in insects such as the honey bee, *Apis mellifera*, using Proboscis extension reflex (PER) conditioning protocols (Chandra et al 2010; 10.1007/s10071-010-0329-6). This procedure involves exposing bees to a four second odor presentation every five minutes for 40 trials. In contrast, a different study, also using honey bees, exposed restrained bees held in small glass vials to a constant odor for an hour (Fernández et al 2012; 10.1101/lm.028167.112). Our objective was to compare results of both methods to evaluate if they reveal the same behavioral processes, which will be important for any field application. After initial exposure to odor - 40 discrete or 1 hour constant - we conditioned bees to two odors, the now familiar odor and a different 'novel' odor. The protocol in Chandra et al produced a strong LI effect, where the novel odor was learned better than the familiar odor. In contrast, the protocol from Fernández et al produced little evidence of learning to either odor. We further tested for evidence of physiological differences between bees exposed to these different protocols. However, we failed to find any differences, leaving still open the reasons for the behavioral differences. The behavioral differences produced by these techniques will have implications for how they can be applied in apiculture to direct and enhance honey bee foraging success.

Disclosures: K.D. Dixon: None. B.H. Smith: None.

Poster

PSTR035: Brain Dynamics of Learning and Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR035.15/W15

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Elucidating errors in translation- operant conditioning in touchscreens across different mouse strains

Authors: *Y. DAS, K. STANGIS, R. NEFF, G. G. MURPHY;

MNI, Univ. of Michigan, Michigan Neurosci. Inst., Ann Arbor, MI

Abstract: Physiological differences observed in animal models are only as meaningful as the behavioral paradigms used to reveal them. Classical learning paradigms like fear conditioning

and Morris Water Maze (MWM), despite their foundational contributions, are limited by their reliance on aversive stimuli and challenges in translational relevance across species. Operant touchscreen-based testing offers a promising alternative: it reduces confounding factors and aligns more closely with human cognitive assessments. The Bussey-Saksida touchscreen system, developed in parallel with the Cambridge Neuropsychological Test Automated Battery (CANTAB), provides a platform for assessing cognitive impairments in neuropsychiatric and neurodevelopmental disorders such as Schizophrenia and Autism Spectrum Disorder. Previous experiments in our lab using transgenic mouse models have employed hippocampal-dependent tasks like location discrimination (LD) and pairwise visual discrimination (PVD), which assess working memory and reversal learning. However, mice failed to complete these tasks in many cases. This was potentially due to insufficient motivation or strain-specific factors. To investigate these issues, we conducted experiments comparing wild-type C57BL/6NTac, B6C3H/F1 hybrids, and sighted C3H strains on LD and PVD tasks. Preliminary results indicate that increased food restriction, changing the operant reward, and shortened session durations significantly improved motivation during pre-training and LD testing. We further assessed motivation and side bias using continuous measures such as reward collection latency, blank touch latency, and the number of blank touches per side. Mice that meet LD criteria will progress to PVD tasks without undergoing pre-training again. Following behavioral training, we will conduct hippocampal analyses of adult neurogenesis. Markers Ki67 and doublecortin (DCX) quantify proliferating progenitors and immature neurons, which will be compared between different strains among mice that complete reversal and those that do not reach criterion. The touchscreen platform minimizes experimenter influence and simplifies behavioral testing, making it accessible to investigators with limited experience or background in behavioral neuroscience. Our findings highlight the importance of controlling for motivational and strain-based variables and establish a framework for linking behavioral outcomes to neurobiological markers in a reproducible and translational model of hippocampal learning.

Disclosures: Y. Das: None. K. Stangis: None. R. Neff: None. G.G. Murphy: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.01/X1

Topic: H.06. Anxiety Disorders

Title: Dysregulated dopaminergic feedback in test anxiety: evidence from the error-related negativity and reward sensitivity

Authors: *E. A. BOURASSA-PRICE¹, H. MATKINS²;

¹Biol. Sci., ²Mississippi Col., Clinton, MS

Abstract: Previous work in our lab has shown that highly test anxious (HTA) students have a smaller error-related negativity (ERN) amplitude on a go/no-go task than students with low test

anxiety (LTA), a finding not seen in other forms of anxiety. Because the ERN is postulated to occur due to a decrease in dopaminergic input to the anterior cingulate cortex (ACC) following an error, we hypothesized that HTA would have decreased reward sensitivity compared to LTA. Also, because anxiety is known to increase the activity of the ventral tegmental area (VTA, one of the major dopaminergic inputs to the ACC), we hypothesized that negative performance feedback would increase the ERN amplitude in HTA but not LTA. To test these hypotheses, 121 participants were screened for test anxiety using the blue-box stress test (BBST), a computerized task developed and validated in our lab; following screening, participants completed a monetary incentive delay task (MID) to measure reward sensitivity. Finally, 32 participants (14 LTA and 18 HTA) were asked to return to the lab to complete a go/no-go task. This was a typical go/no-go task, except that following task completion, participants repeated the go/no-go task while performance feedback was provided. Participants were told their performance was calculated as their performance relative to a standard population; however, all participants received the same, negative (<25th percentile) feedback. During both phases of the go/no-go task, continuous 9-lead electroencephalography was recorded. HTA had faster reaction times than LTA on both phases of the go/no-go task, and reaction times in both groups were significantly faster when negative feedback was given. Although there was no significant difference in error rates between LTA and HTA on either phase of the go/no-go task, the error rate was significantly lower when negative feedback was given. Consistent with previous findings in our lab, the ERN was significantly smaller in HTA compared to LTA when no performance feedback was provided. In line with our hypothesis, negative performance feedback significantly increased the amplitude of the ERN in HTA, but not LTA. On the MID, the ratio of task performance on high-reward relative to high-loss trials was calculated, which showed a significant negative correlation with BBST scores ($r = -0.305$, $p = 0.0003$), consistent with the hypothesis that HTA have reduced reward sensitivity compared to LTA. Taken together, these findings suggest that a test anxiety is distinct from other forms of anxiety and is at least partially characterized by a dysregulated dopaminergic circuit between the VTA and ACC.

Disclosures: E.A. Bourassa-Price: None. H. Matkins: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.02/Web Only

Topic: H.06. Anxiety Disorders

Support: The National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) No. 2019R1A2C1086581
The National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) No. RS-2023-00265883

Title: Interconnecting role of comorbid depressed mood and general anxiety in the symptom network of social anxiety disorder

Authors: *M. KIM¹, T. KIM¹, J. LEE¹, S. HONG², S. KWAK¹, D. LEE¹, D. KANG³, S.-H. CHOI^{4,1};

¹Dept. of Psychiatry, Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; ²Weldon Sch. of Biomed. engineering, Purdue Univ. Col. of Engin., West Lafayette, IN; ³Dept. of Psychiatry, Wonkwang Univ. Sanbon Hosp., Gyeonggi-do, Korea, Republic of; ⁴Dept. of Psychiatry, Seoul Natl. Univ. Col. of Med. and Inst. of Human behavioral Medicine, SNU-MRC, Seoul, Korea, Republic of

Abstract: Social anxiety disorder (SAD) is often comorbid with depression and general anxiety symptoms, intensifying symptom severity and functional impairment. However, the dynamic interactions among these symptom domains within SAD remain unclear. We aimed to delineate the interconnections among social anxiety, depressed mood, general anxiety, and functional impairment using a network analytic approach.

A total of 81 patients with SAD (45 females; mean age of 24.8 years) and 89 healthy controls (42 females; mean age of 24.9 years) completed self-report measures assessing social anxiety (Liebowitz Social Anxiety Scale and Fear of Negative Evaluation Scale), depression (Beck Depression Inventory), general anxiety (Beck Anxiety Inventory), and functional impairment (Sheehan Disability Scale). Eight symptom nodes were derived based on factor analysis and categorized into three clusters: social anxiety, comorbidity, and functional impairment. We constructed a Gaussian Graphical Model (GGM) to identify central and bridging symptoms, and a Directed Acyclic Graph (DAG) to examine directional dependencies, with model regularization and bootstrapped stability assessments to ensure statistical robustness.

In the SAD group, performance anxiety emerged as the upstream origin from which all other symptom dimensions propagated. Alongside its upstream role, performance anxiety, affective depression, and psychic anxiety exhibited the highest centrality and bridging influence within the network. Notably, psychic anxiety served as a key bridge, linking social anxiety symptoms with both comorbid and functional impairment clusters. DAG analysis revealed a directional cascade in which performance anxiety led to affective depression, which in turn influenced psychic anxiety. Psychic anxiety subsequently contributed to both functional impairment and fear of negative evaluation. In contrast, the control group showed weak symptomatic connections and limited propagation, with minimal probabilistic dependency observed between social anxiety symptoms and comorbid domains.

These findings suggest that performance anxiety may initiate the progression of other symptoms in SAD, leading to comorbidity through depressed mood and psychic anxiety symptoms. Psychic anxiety, in particular, emerged as a key bridge linking social anxiety to comorbid depression and general anxiety symptoms. These results clarify how symptom domains in SAD are interconnected and deepen our understanding of comorbidity mechanisms and functional impairment, offering insights that may guide treatment strategies to prevent the development of SAD and its comorbidities.

Disclosures: M. Kim: None. T. Kim: None. J. Lee: None. S. Hong: None. S. Kwak: None. D. Lee: None. D. Kang: None. S. Choi: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.03/Web Only

Topic: H.04. Emotion

Support: MVP is supported by Special Chair "Doctor Bernardo Sepúlveda Gutiérrez," awarded by the Technical Council of the Faculty of Medicine from August 2024 to 2025.
LGV is supported by the "Postdoctoral Fellowships in National Institutions" program from CITNOVA

Title: The impact of a mindfulness-based intervention on burnout syndrome and the related biochemical and cognitive biomarkers in a medical university population

Authors: *M. VELAZQUEZ-PANIAGUA^{1,2}, L. GÓMEZ³, M. GÓMEZ-CHAVARÍN⁴, R. SAMPIERI-CABRERA⁵;

¹UNAM, CDMX, Mexico; ²Dept. of Physiology, Prospective Lab., Med. School, UNAM, Mexico city, Mexico; ³Facultad de Medicina, CDMX, Mexico; ⁴Physiol., UNAM Biomed. Res. Inst., Mexico City, Mexico; ⁵Dept. of Physiology, Fac. of Medicine, Natl. Autonomous Univ. of Mexico, Mexico City, Mexico

Abstract: Abstract In Mexico, between 25% and 45% of medical students experience burnout syndrome. Mindfulness-based interventions (MBIs) may alleviate this condition. To date, no study has been conducted in the country to evaluate the effect of such interventions on this population. Objective: To determine the effects of an eight-week Mindfulness-Based Stress Reduction (MBSR) program applied to medical students and university staff. Method: A quasi-experimental design was employed, incorporating pre- and post- intervention assessments. A total of 38 participants completed the MBSR program, and its effects were evaluated across psychological, biological, and neurophysiological indicators. Statistical analysis was performed using the paired Student's t-test and the Wilcoxon test. Results: The average age was 28, and 84% of participants were women. First-year students accounted for 24% of the sample. The intervention yielded significant effects on cortisol levels ($p < 0.001$), all three dimensions of burnout syndrome—emotional exhaustion ($p < 0.001$), depersonalization ($p = 0.008$), and personal accomplishment ($p < 0.001$)—as well as on P300 amplitude ($p < 0.05$). Conclusions: The mindfulness-based intervention reduced burnout syndrome, lowered cortisol levels, and influenced neurophysiological parameters.

Disclosures: M. Velazquez-Paniagua: None. L. Gómez: None. M. Gómez-Chavarín: None. R. Sampieri-Cabrera: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.04/X2

Topic: H.04. Emotion

Support: Fondazione Cassa di Risparmio di Firenze: CUP G95F21000150007
(Human Brain Optical Mapping)

Title: Multispectral Optical Sensing of Stress Responses in Human Skin

Authors: *V. BARYGINA¹, E. BARIA¹, E. CRAVERO², F. GORETTI³, F. S. PAVONE¹;
¹Univ. of Florence, Firenze, Italy; ²Univ. Campus Biomedico of Rome, Rome, Italy; ³European
Lab. for Non-Linear Spectroscopy, Sesto Fiorentino, Italy

Abstract: Skin matrices—such as skin tissue, interstitial fluid, and sweat—represent important sources of molecular biomarkers for physiological and psychological states. Moreover, several unique biomarkers are found exclusively in skin interstitial fluid. However, the analysis of the molecular composition of interstitial fluid is a time-consuming, invasive or semi-invasive, and costly process. In this study, we aimed to identify stress-related skin responses using a high-throughput, multimodal combination of optical techniques. Raman, reflectance, and fluorescence spectra, together with spectrally-resolved fluorescence decays—for a total of 21 spectral and time curves per sample—were recorded from the palm skin of healthy volunteers using a multimodal fiber-probe device. To induce psychological stress, participants underwent the Montreal Imaging Stress Task (MIST), after which a second set of spectral data was collected. Electrodermal activity, heart rate, and heart rate variability were monitored throughout the experiment to validate the induction of psychological stress. The multimodal approach achieved 100% accuracy in classifying “no-stress” versus “stress” conditions. Several Raman spectral shifts were observed in the stress (STR) group compared to the control (CTRL) under our experimental conditions. To correlate these spectral changes with specific stress-related biomolecules, we began constructing a reference database of Raman, reflectance, fluorescence, and fluorescence lifetime spectra for key molecular targets. Spectral data were acquired from pure molecules including IL-1 α , IL-1 β , IL-6, IL-8, TNF- α , cortisol, and neuropeptide Y. We are currently evaluating the use of a convolutional neural network (CNN) for spectral unmixing. Preliminary results confirm the potential of our multispectral optical sensor for the non-invasive detection of psychological stress.

Disclosures: V. Barygina: None. E. Baria: None. E. Cravero: None. F. Goretti: None. F.S. Pavone: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.05/X3

Topic: H.03. Motivation

Support: NIH R01MH119086

Title: Multidimensional aspects of fatigue during isolated and whole-body movements: A feasibility study

Authors: *A. KIM^{1,3}, R. T. ROEMMICH^{2,3}, V. S. CHIB^{1,3};

¹Biomed. Engin., ²Physical Med. and Rehabil., Johns Hopkins Univ., Baltimore, MD; ³Kennedy Krieger Inst., Baltimore, MD

Abstract: Fatigue is a common and disruptive symptom in both healthy individuals and those with neurological conditions, often impairing daily functioning. Fatigue is a symptom that spans across different types of effort (e.g., arm movements, walking, cognitive exertion). While previous studies have primarily focused on isometric hand contraction paradigms to examine the multidimensional nature of fatigue, it remains unclear whether findings from isolated hand movements directly translate into more ecologically valid, whole-body activities such as walking. In this study, we examine how three potential aspects of fatigue — affect (feelings of tiredness), sensorimotor perception (effort perception), and value (effort cost) — manifest across both grip exertion and walking.

We had 27 participants complete two fatigue-inducing paradigms on separate days: (1) an isometric hand contraction task (GRIP) with effort manipulated via grip force normalized to individual maximum voluntary contraction; and (2) a treadmill walking task (WALK) with effort manipulated via increasing inclines. In GRIP, participants performed 11 blocks of repeated exertion (~30 mins), during which we continuously surveyed ratings of tiredness and effort perception and intermittently assessed effort cost through effort-based decision-making. In WALK, participants completed 8 incline walking blocks (~32 mins), reporting identical measures.

Both paradigms successfully elicited progressive increases in feelings of tiredness (GRIP and WALK: $p < 0.001$), with all participants completing both sessions, thereby supporting the feasibility and effectiveness of the interventions. Effort perception also increased in both tasks (GRIP and WALK: $p < 0.001$), indicating that repeated exertion led to increased perceived effort. However, the changes in feelings of tiredness and effort perception were not correlated across movements, suggesting that these aspects of fatigue may be task-specific and mediated by distinct mechanisms. In contrast, effort costs remained stable even after repeated exertion within each movement. Still, they showed a strong correlation between GRIP and WALK during baseline ($r = 0.72$, $p < 0.001$) and changes over time ($r = 0.55$, $p = 0.01$). These results indicate the presence of shared value-based processes across various exertion contexts. These findings offer critical insight into the multidimensional nature of fatigue and highlight the importance of assessing fatigue beyond isolated tasks.

Disclosures: A. Kim: None. R.T. Roemmich: None. V.S. Chib: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.06/X4

Topic: H.04. Emotion

Title: Mindfulness Attenuates Physiological Stress Following Negative Mood Induction

Authors: *A. M. CAMPOS¹, G. BATCHALLI MARUTHY¹, G. CUMMING¹, S. RODRIGUEZ¹, J. GUERRERO¹, J. BROOKS¹, B. RYPMA²;

¹The Univ. of Texas at Dallas, Richardson, TX; ²Behavioral & Brain Sci., The Univ. of Texas At Dallas, Richardson, TX

Abstract: Cortisol supports physiological stress-responses by promoting glucogenesis and amino acid release, but over- or under-production impairs emotion regulation of anxiety, depression, and negative mood (e.g., sadness). While research in mindfulness has consistently shown benefits for reducing perceived stress, physiological mechanisms are not yet well understood. In forty-eight participants (age range = 19 to 81 years old, 13 males, 35 females), we assessed relationships between mindfulness, as measured by the Five-Facets Mindfulness Questionnaire (FFMQ), stress as measured by cortisol (following mood induction), and cognitive performance as measured in the Attention Network Task (ANT). Data included questionnaires (FFMQ, stress, emotion regulation), mood, and the ANT. Stress was induced by negative mood induction. Negative affect was induced through a combination of somber music and self-referential prompts designed to elicit rumination on past negative experiences. Cognition was measured at baseline and after mood induction using the ANT. Mood was measured at four time points: 1) baseline, 2) after induction, 3) after the ANT, and 4) near completion of study. Cortisol was measured at two points, baseline and after mood induction. Data were drawn from a subset of twenty participants (age range = 20 - 81, 4 males, 16 females) who provided cortisol saliva samples as part of a larger meditation training study. Spearman Rank-Order correlations were performed to assess the monotonic associations between cortisol and mood, mindfulness, behavior, and cognitive performance. In general, results indicated that reduced cortisol stress responses were associated with increased mindfulness, reappraisal strategies, and reduced reports of cognitive suppression. In particular, observing and describing facets were related to reduced or attenuated physiological stress responses to the negative mood induction procedure. Greater elevation of cortisol was associated with more pronounced declines in happiness, decreased orienting (i.e., ability to switch attention in the task), increased alertness, and slower reaction times after the negative mood induction. Poorer reappraisal was associated with increased alertness and orienting but reduced executive functioning. Mindfulness and emotion regulation may modulate the physiological stress response, as indexed by cortisol, with downstream implications for cognitive function.

Disclosures: A.M. Campos: None. G. Batchalli Maruthy: None. G. Cumming: None. S. Rodriguez: None. J. Guerrero: None. J. Brooks: None. B. Rypma: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.07/X5

Topic: H.08. Drugs of Abuse and Addiction

Title: Cortical thickness as a mediator of the association between age of first alcohol use and delay discounting

Authors: *M. SINCLAIR¹, N. J. BUSH¹, J. BOISSONEAULT²;

²Anesthesiol., ¹Univ. of Minnesota, Minneapolis, MN

Abstract: Background: Early initiation of alcohol use is linked to greater risk for alcohol use disorder, reduced cortical thickness and gray matter volume, and neurocognitive impairment. Gray matter disruption has been previously associated with greater delay discounting (DD), which quantifies an individual's preference for smaller immediate rewards compared to larger delayed rewards. Greater DD has been linked to higher risk for negative health outcomes. This study investigated whether age of initiation of drinking may influence DD indirectly through its effects on cortical thickness.

Method: Participants in the Human Connectome Project endorsing lifetime alcohol use (N=1018, Mage=28.79 years, 53.7% female, 75.8% white, 89.7% non-Hispanic or Latino/x/e) completed hypothetical DD tasks determining preference for lower value immediate monetary rewards vs. larger delayed rewards (\$200 and \$40k). DD was quantified as area under the curve (AUC), with lower AUC reflecting greater DD. 12.1% of participants initiated alcohol use prior to age 15, 24.5% from 15-16, 28.6% from 17-18, 13.4% from 19-20, and 21.5% after age 21. T1-weighted structural MRI scans were parcellated and cortical thickness was calculated using FreeSurfer v5.3. Bootstrap mediation analysis determined the indirect effect of age of initiation on DD through cortical thickness of regions associated with age of initiation. Sex, age, total intracranial volume, and income were included as covariates.

Results: Age of initiation of alcohol use was not significantly correlated with DD AUCs ($p>.68$). However, age of initiation had a significant indirect effect on the \$40,000 ($b=.001$, 95% CI: .0000-.0027) and \$200 ($b=.0008$, 95% CI: .0000-.002) DD AUCs through fusiform gyrus thickness. Similarly, age of initiation of alcohol use had a significant indirect effect on the \$40,000 ($b=.001$, 95% CI: .0000-.0027) and \$200 ($b=.0008$, 95% CI: .0000-.0021) DD AUCs through posterior cingulate thickness. Greater cortical thickness of the cuneus ($\beta=.1839$, $p<.05$) and lateral occipital cortex ($\beta=.1948$, $p<.05$) were significantly related with higher \$40,000 DD AUC, although the indirect effect of age of initiation was not significant. No significant direct or indirect effects were noted for any other region examined.

Conclusion: Cortical thickness was a significant mediator of the effect of age of alcohol initiation on DD for fusiform gyrus and posterior cingulate. In each case, later age of initiation was associated with greater cortical thickness, which in turn predicted higher DD AUC. Overall, results indicate that age of initiation of alcohol use may impact DD indirectly through its effects on brain structure.

Disclosures: M. Sinclair: None. N.J. Bush: None. J. Boissoneault: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.08/X6

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH: R01AA025337-01A1

Title: Change in NAc-MTL functional connectivity as a mediator of the association between pain-related anxiety and alcohol-induced pain relief

Authors: *A. BELHE¹, L. SEVEL², J. BOISSONEAULT²;

¹Neurosci., ²Anesthesiol., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Alcohol analgesia is a potent negative reinforcer of alcohol intake in people with pain. This interrelationship between pain and alcohol use lies at the intersection of multiple biopsychosocial factors, including pain-related anxiety. Notably, aberrant nucleus accumbens (NAc) function has been implicated in the development of chronic pain and regulation of pain-related anxiety. Acute alcohol intake results in subjective pain relief that might be modulated by pain-related anxiety through effects on NAc function, known primarily for its role in reward and motivated behavior. The overall aim of this study was to determine whether alcohol-induced change in pain-related NAc functional connectivity (Δ FC) mediates the association between pain-related anxiety and alcohol-induced pain relief.

To investigate this aim, 99 healthy volunteers between the ages of 21-45 years completed two laboratory sessions in which they were administered one of two beverages: placebo (0.00 g/dL target breath alcohol concentration (BrAC)) or active alcohol (0.08 g/dL target BrAC). Three task-based fMRI runs were then conducted with a noxious thermal stimulus delivered to the glabrous skin of the foot using an MR-compatible thermal probe. After each run, participants rated their perceived pain relief as a result of consuming their beverage using an electronic visual analog scale (VAS). Pain-related anxiety was assessed using the PASS-20 questionnaire. The association of PASS-20 scores with the effect of alcohol on pain-related FC of the NAc with the rest of the brain was evaluated using the generalized psychophysiological interaction (gPPI) pipeline within the CONN Toolbox. A bootstrap mediation analysis using the PROCESS macro package in SPSS (10000 samples with 95% confidence interval) was then conducted to determine whether Δ FC of the NAc mediated the relationship between PASS-20 and pain-relief ratings.

Overall, higher PASS-20 scores were associated with stronger Δ FC between the NAc and a cluster within the medial temporal lobe (MTL) (+54, -54, +04; $k = 128$; $p\text{-FDR} = 0.008$), a region implicated in both the emotional modulation of experimental pain and the development of chronic pain. Additionally, bootstrap analysis revealed that the NAc-MTL Δ FC significantly mediated the association of pain-related anxiety with perceived pain relief ($\beta = -0.30$; Boot: LLCI = -0.5183, ULCI = -0.1267). Taken together, these results suggest that pain-related anxiety influences alcohol-induced pain relief through changes in pain-related NAc-MTL FC, consistent with an important role of reward and motivation-related networks in understanding self-management of pain using alcohol.

Disclosures: A. Belhe: None. L. Sevel: None. J. Boissoneault: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.09/X7

Topic: H.06. Anxiety Disorders

Title: Determination of biochemical parameters in a population with depression and anxiety from western Mexico

Authors: *A. GONZALEZ AVALOS¹, L. BECERRA-SOLANO², M. MACÍAS-CARBALLO³;

¹Ctr. Universitario de los Altos, Univ. de Guadalajara, Tapatitlan de Morelos, Mexico; ²Dept. de clínicas, Univ. de Guadalajara, Tapatitlan de Morelos, Mexico; ³Dept. de clínicas, Univ. de Guadalajara, Tapatitlán de Morelos Jalisco, Mexico

Abstract: Depression and anxiety are multifactorial disorders with high prevalence. The influence of certain biochemical parameters such as glucose, triglycerides, and cholesterol has been reported; elevated levels of depression and anxiety have been associated with high glucose levels, while lower levels of depression and anxiety have been associated with high cholesterol levels. We determinate levels of depression and anxiety, as well as glucose, cholesterol, and triglycerides. We included 258 individuals. The State-Trait Anxiety Inventory and the Beck Depression Inventory-Second Edition were applied to measure their levels of depression and anxiety. The results showed that most participants presented with minimal level depression, 137 (53.1%), although 34 (13.2%) had severe level depression. In another hand, for Trait Anxiety, the medium level was the most Trait Anxiety, with 128 participants (49.6%), while for State Anxiety, the high level was most frequent with 140 participants (54.3%). Biochemical parameters were analyzed using the CHEM-7 Erba Mannheim® device with specific reagents for each parameter (Biosystem®). A stratified analysis was conducted comparing biochemical parameters between those with minimal/mild vs. moderate/severe depression. Statistically significant differences were found in triglyceride levels ($p = 0.032$), being higher in the moderate/severe level group. Similarly, anxiety groups were categorized into Minimal level vs. Moderate/Severe level for both Trait and State Anxiety. No statistically significant differences were found for Trait Anxiety; however, for State Anxiety, significant differences were found in glucose levels ($p = 0.049$), with higher levels in the minimal level Anxiety group. These findings suggest that biochemical markers may be linked to symptomatology; however, further studies are needed to describe the underlying mechanisms. This study was conducted in accordance with the Mexican Official Standard NOM-012-SSA3-2012.

Disclosures: A. Gonzalez Avalos: None. L. Becerra-Solano: None. M. Macías-Carballo: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.10/X8

Topic: H.06. Anxiety Disorders

Title: Eeg frequency patterns as an emotional burnout brain signature

Authors: *S. TUKAEV¹, J. ALVES FERREIRA²;

¹Natl. Taras Shevchenko Univ. of Kyiv, Educational Scientific Inst. of High Technologies, Kyiv, Ukraine; ²Faculdade de Medicina, Univ. de Coimbra, Coimbra, Portugal

Abstract: Burnout develops gradually and often goes unnoticed, with symptoms that may take years to manifest and lead to significant mental and behavioral changes. Despite its impact, the processes underlying burnout remain largely unknown due to a lack of specialized studies identifying specific biomarkers. Early detection of burnout, particularly at the critical onset of symptoms, is essential. This study aimed to examine functional connectivity changes associated with the severity of the Anxiety-Tension stage of Emotional Burnout. A total of 752 participants, including students and staff from Taras Shevchenko National University of Kyiv (209 males, mean age = 19.2; 543 females, mean age = 18.28), were assessed using the 84-item Boyko's Syndrome of Emotional Burnout Inventory. EEG data were recorded during a 3-minute resting state with eyes closed, and artifact-free segments from all frequency bands (0.2-45 Hz) were analyzed. Normalized power spectral densities (PSD) and coherence were calculated, focusing on the 61-70 second segment of the recordings. The results revealed burnout-related changes in spectral characteristics associated with the Anxiety-Tension stage, with significant alterations observed in the theta 2 band (frontal and left temporal-parietal cortex), alpha 2 band (right parietotemporal cortex), and beta 1 band (left frontal-central-right parietal axis). Coherence analysis complemented the spectral findings, highlighting alpha band synchronization in frontal and parietal areas, which supports visuospatial attention and memory processes. In contrast, desynchronization in high beta and gamma bands indicated disrupted connectivity, affecting higher-order cognitive functions. These findings suggest that the Anxiety-Tension stage primarily impacts processes related to short-term memory and focused attention, providing a potential framework for the early identification of burnout through neurophysiological markers.

Disclosures: S. Tukaev: None. J. Alves Ferreira: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.11/X9

Topic: H.04. Emotion

Support: National Institutes of Health
Vada Kinman Oldfield Award Funds
NIGMS COBRE Award #: P20GM13044701A1

Title: Investigating Different Subtypes of Social Support and Relationships with Cortisol Reactivity due to a Social Stressor

Authors: *V. M. SLOTTERBACK¹, J. N. BEADLE²;
²Gerontology, ¹Univ. of Nebraska Omaha, Omaha, NE

Abstract: It is well-established that in healthy adults social stressors can temporarily elevate cortisol levels which eventually return to baseline. Yet, individuals with high levels of chronic stress may experience blunting of their cortisol response to stressors or a slower return to baseline. Social support may be helpful in regulating cortisol during stressful encounters. However, less is known about how different subtypes of social support can differentially affect cortisol reactivity to a social stressor, especially across the lifespan. We hypothesized that emotional/informational support may be associated with cortisol reactivity levels because this type of support is closely linked to strong social bonds. We investigated different types of social support and cortisol reactivity in response to a newly developed virtual Trier Social Stress Test (vTSST) in a sample of healthy adults aged 19-86 (N=54; Mage=55.85; Medu=16.09; 64.8% female). Participants completed the 19-item Social Support Survey Instrument (Rand Corporation), which measured different subtypes of social support: Emotional/Informational Support (EIS), Tangible Support (TS), Affectionate Support (AS), and Positive Social Interaction (PSI). Salivary cortisol was collected using the passive drool method at baseline and 20 minutes post social stressor in response to the vTSST. We conducted a regression model investigating the relationship between the EIS subtype of social support and 20-minute post-induction cortisol levels, while accounting for age, gender, and baseline cortisol levels. The regression model was significant ($F(4,49)=p<.05$; $r\text{-squared}=.18$). EIS was significantly, positively associated with 20-minute post-induction cortisol levels ($\text{Beta}=.29$; $p=.039$). Gender was significantly and positively associated with 20-minute post-induction cortisol levels ($\text{Beta}=.28$; $p=.043$). Age and baseline cortisol levels were not significantly associated with 20-minute post-induction cortisol. The other subtypes were not significantly associated with 20-minute post-induction cortisol levels. Higher EIS may be linked to greater cortisol reactivity because it may reflect a healthier stress response compared to the blunted patterns often seen in individuals under chronic stress. Emotionally supportive relationships may buffer the effects of stress. Consistent with prior research, men exhibited greater cortisol reactivity than women, as men may rely less on social coping strategies than women. Future research is needed to replicate these findings using in-person stress tasks and longitudinal designs to further elucidate these mechanisms.

Disclosures: V.M. Slotterback: None. J.N. Beadle: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.12/Web Only

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA Grant R01AA028225

Title: Changes in binge drinking and associations with behavioral and neural reactivity to threat in youth

Authors: *A. N. HOUSE^{1,2}, K. C. JENKINS^{1,2}, K. A. KREUTZER^{1,2}, J. JIMMY¹, B. WAY⁴, S. CULP³, S. CHANDRASENA³, K. PHAN¹, S. M. GORKA^{1,2};

¹Dept. of Psychiatry and Behavioral Hlth., ²Inst. for Behavioral Med. Res., ³Dept. of Biomed. Informatics, The Ohio State Univ. Wexner Med. Ctr., Columbus, OH; ⁴Dept. of Psychology, The Ohio State Univ., Columbus, OH

Abstract: Heightened behavioral and brain reactivity to uncertain threats (U-threat) is associated with increased risk for problematic alcohol use, including alcohol use disorder (AUD). Although studies have linked elevated U-threat reactivity to greater AUD severity and coping-related drinking motives, it is still unclear whether this heightened response remains stable over time, particularly as adolescents begin drinking. Prior research suggests that increased U-threat reactivity may contribute to the development of binge drinking in youth, but it unknown whether this represents a fixed risk factor or a modifiable target for the prevention and treatment of excessive alcohol use. The present study aimed to fill this gap in the literature by examining whether changes in drinking behavior correspond with changes in behavioral and neural reactivity to U-threat in youth, ages 16-19. A total of 137 participants completed the well-validated No Threat-Predictable Threat-Unpredictable Threat (NPU) task both inside and outside the neuroimaging scanner at baseline and again 6-months later. During functional magnetic resonance imaging (fMRI), activation of the anterior insula (aINS) was used to index reactivity to U-threat, while startle eyeblink potentiation served as a behavioral measure of U-threat reactivity. Participants completed self-report surveys tracking drinking behaviors over the past 90-days and frequency of binge drinking was estimated at baseline and 6-months. A multilevel linear mixed model was used to examine whether change in frequency of binge drinking was associated with change in behavioral and brain measures of U-threat reactivity. Biological sex, age, and exposure to early life trauma (yes/no) were entered as fixed covariates. Change in anxiety symptom severity and change in frequency of cannabis use were also included in the model. Results revealed that there was a significant time by change in binge drinking interaction on startle reactivity to U-threat ($F[1, 124] = 4.08, p = .04$). At increased levels of binge drinking, there was a significant increase in startle reactivity to U-threat; however, at decreased levels of binge drinking, there was no change. Notably, there was no significant time by change in binge drinking interaction on aINS activation during U-threat. These findings suggest that behavioral reactivity to U-threat is modifiable and changes as drinking patterns emerge. In contrast, neural reactivity to U-threat, as measured by aINS activation, may be less sensitive to early changes in binge drinking. This indicates that neural adaptations could lag behind behavioral changes in the initial stages of problematic alcohol use.

Disclosures: A.N. House: None. K.C. Jenkins: None. K.A. Kreutzer: None. J. Jimmy: None. B. Way: None. S. Culp: None. S. Chandrasena: None. K. Phan: None. S.M. Gorka: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.13/X10

Topic: H.04. Emotion

Title: Gut Feelings: Negative Affect Enhances Brain-Body Coupling

Authors: *A. YOUNG¹, S. BAUMGART¹, J. RIDDLE², J. W. SCHOOLER¹;

¹Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA;

²Psychology, Florida State Univ., Tallahassee, FL

Abstract: Visceral and cognitive processes have long been theorized to co-regulate one another with early frameworks such as the James-Lange theory of emotion, which proposed that emotional experience emerges from the perception of bodily states. The present study examines how brain-body synchrony, operationalized by transient frequency alignment or “harmonic locking,” between EEG and cardiovascular rhythms is modulated by emotional valence in simultaneous EEG and physiological recordings. We find that negative affect, but not positive affect, is associated with enhanced coupling of EEG and cardiovascular rhythms. Follow-up analyses identified item-level correlates (e.g. “Afraid”) indicating brain-body synchrony is driven particularly by fight-or-flight phenomenology. Theta frequency was found to couple to cardiovascular rhythms and higher frequency EEG bands coupled to theta, indicating a nested, hierarchical organization whereby the network-level, scaffolding oscillations of the brain are in turn scaffolded by the physiology as a function of negative affect. Together, the results indicate that emotional states -particularly those evoking threat- dynamically promote a nested, hierarchical organization of brain and body rhythms.

Disclosures: A. Young: None. S. Baumgart: None. J. Riddle: None. J.W. Schooler: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.14/X11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH: R01AA025337-01A1

Title: Placebo Efficacy Modulates Perceived Pain Relief but Not Pain Sensitivity in a Double Blind Alcohol Administration Paradigm

Authors: *A. CUSHNIE¹, N. BUSH¹, L. SEVEL¹, J. BOISSONEAULT²;
²Anesthesiol., ¹Univ. of Minnesota, Minneapolis, MN

Abstract: Pain is an aversive experience, comprising sensory, affective, and cognitive components. Numerous therapeutic strategies are available for pain management, including opioid analgesics; however, treatment efficacy varies considerably between individuals and frequently falls short of patient-defined success criteria. As a result, many patients report at least occasional use of alcohol for pain self-management. Laboratory studies indicate that alcohol has analgesic effects and is associated with the perception of pain relief. However, the role of non-specific effects mediated by experiences and expectations (i.e., placebo) in producing alcohol analgesia is not well understood. Empirical evidence indicates that placebo analgesia can attenuate pain through nonspecific psychosocial mechanisms, highlighting the significance of cognitive and contextual influences on pain experience. We hypothesize that perceived pain intensity and pain relief would be modulated by participants' beliefs about whether they received an alcoholic beverage.

Healthy adults (N=99, M=26.2 age (SD=4.91), 42.42 % FH+) completed a counterbalanced study, either an alcoholic or a placebo beverage was administered, followed by heat-based quantitative sensory testing (QST) to assess pain threshold, pain tolerance, and suprathreshold pain intensity. Using ANOVA, we examined the effect of believing one received alcohol on QST outcomes, subjective intoxication (SI), and perceived pain relief during placebo sessions. 41.81% of participants reported believing their drink contained alcohol. Participants who believed that their beverages contained alcohol reported significantly higher SI ratings ($F_{1,91}=41.369, p<0.001, \eta_p^2=0.313$). SI was strongly correlated with self-reported pain relief ($r = 0.782, p < .001$), but it was not significantly related to pain intensity ratings ($r = .130, p = .2$) and participants who believed they had consumed alcohol reported greater pain relief overall ($F_{(1,91)} = 19.22, p < .001, \eta_p^2 = .174$). However, as with SI, reported pain relief was not significantly associated with pain ratings ($r = .069, p = .497$). Belief of receiving alcohol was also not associated with pain intensity; pain threshold ($F_{(1,91)} = 0.674, p = 0.414, \eta_p^2 = 0.007$ or pain tolerance ($F_{(1,91)} = 2.902, p = 0.092, \eta_p^2 = 0.031$).

Belief that one received alcohol was significantly associated with greater SI and pain relief, but not pain sensitivity or intensity. SI was strongly correlated with pain relief, but not with pain intensity. These results underscore the role of placebo in shaping alcohol's negative reinforcing effects when used in the context of pain self-management.

Disclosures: A. Cushnie: None. N. Bush: None. L. Sevel: None. J. Boissoneault: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.15/X12

Topic: H.08. Drugs of Abuse and Addiction

Support: Binge Grant: R21 AA027371
San Diego State University

Title: Hidden Neural Costs of Binge Drinking: Compensatory Frontal Activation and Connectivity During Cognitive Control in Young Adults

Authors: *A. SIMARD^{1,2}, D. WHITE¹, A. B. ALDERSONMYERS^{1,3}, K. MARINKOVIC²;
²Psychology, ¹San Diego State Univ., San Diego, CA; ³Radiology, Univ. of California San Diego, San Diego, CA

Abstract: Binge drinking is common among young adults and refers to instances of heavy drinking interspersed with periods of sobriety or low intake. A binge episode is defined as consuming 4+/5+ drinks for women/men in two hours. Models of addiction propose that impaired cognitive control underlies the inability to refrain from hazardous drinking, which may contribute to developing alcohol use disorder. Essential for flexible and adaptive decision-making, cognitive control is an executive function that relies on the capacity to suppress automatic responses in favor of goal-relevant actions. Despite the high prevalence of binge drinking, evidence of behavioral deficits and neural alterations related to compulsive intermittent alcohol consumption is scant, and our knowledge of biological sex differences is rudimentary. To address these research gaps, the present study aimed to examine neurobehavioral indices of cognitive control in a large group (N = 75) of young, healthy women and men differing in their alcohol intake. They were classified as binge drinkers (BDs = 35) or light drinkers (LDs = 40) if they reported engaging in ≥ 5 or ≤ 2 binge episodes in the past six months, respectively. The groups were matched on demographic variables, cognitive ability, and family history of alcoholism. Participants underwent functional magnetic resonance imaging (fMRI) scans while performing the Stroop task, commonly used to probe cognitive control. BDs and LDs did not differ in task performance. However, voxel-wise analysis of the fMRI data (AFNI) revealed higher brain activity in BDs than in LDs in the anterior cingulate cortex (ACC) during high-conflict trials. This group effect was driven by the difference between BD and LD women, which is relevant to women's greater cognitive vulnerability to alcohol misuse. Preliminary analysis (CONN) revealed increased functional connectivity in BD women between the seeds in the ACC and the right inferior frontal cortex and the prefrontal cortices. The enhanced brain activation and connectivity patterns suggest compensatory neural mechanisms whereby BDs recruit additional prefrontal resources to maintain normative task performance during cognitive conflict. Suggestive of deficient decision-making, these results are consistent with altered neurocognitive functioning due to alcohol misuse at this early stage of alcohol consumption. They contribute to understanding the neural dysregulation associated with excessive drinking in young adult BDs. This evidence confirms greater women's vulnerability to alcohol and could inform early detection and development of interventions targeting cognitive control and binge drinking.

Disclosures: A. Simard: None. D. White: None. A.B. Aldersonmyers: None. K. Marinkovic: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.16/X13

Topic: H.06. Anxiety Disorders

Support: IBRO / Wellcome Trust - IW-6594875598

Title: Electrophysiological underpinnings of empathy for pain in anxious and non-anxious university students

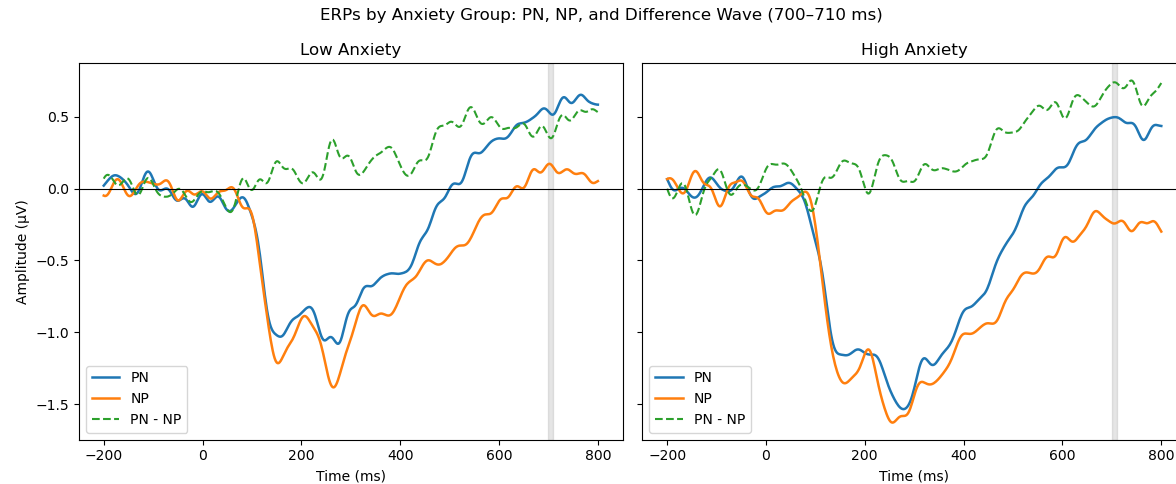
Authors: *L. V. SÁNCHEZ-VINCITORE¹, M. E. CASTELLO², J. DUÑABEITIA⁴, F. ROMERO³, F. MOREIRA³, H. MARTE-SANTANA¹;

¹Lab. de Neurocognición y Psicofisiología, Univ. Iberoamericana, Santo Domingo, Dominican Republic; ²Neurociencias Integrativas y Computacionales, ³Inst. de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay; ⁴Univ. Nebrija, Madrid, Spain

Abstract: Empathy for others' pain engages both early attentional and later affective processes, which may be modulated by individual differences in anxiety. This study examined whether anxiety influences neural responses to others' pain using event-related potentials (ERPs). Forty-four undergraduate students (M = 20.63 years, SD = 2.36; 43.2% women) from a private university in Santo Domingo, Dominican Republic, completed an Empathy for Pain Task while EEG was recorded using a 128-channel EGI system. Anxiety was assessed via the Generalized Anxiety Disorder 7-item scale; participants were classified into high/low anxiety groups. The task involved 256 images of hands and feet in painful or non-painful scenarios. Participants judged whether each image represented a painful situation. ERP analysis examined spatiotemporal dynamics using cluster-based permutation testing. Forty-one significant clusters ($p < .05$), mainly over centro-parietal, parieto-occipital, and midline frontal regions, differentiated painful (PN) from non-painful (NP) stimuli. Many emerged between 460-799 ms post-stimulus, consistent with the Late Positive Potential (LPP), an index of sustained emotional processing.

To reduce dimensionality, robust clusters were averaged into a region of interest and time window (460-799 ms). Mean amplitudes were significantly more positive for PN than NP trials, $t(44) = 5.91$, $p < .0001$ ($\Delta M = 0.50 \mu V$, $SD = 0.56$). Difference waves (PN-NP) were compared between anxiety groups. The high-anxiety group ($n = 19$) showed significantly greater LPP positivity than the low-anxiety group ($n = 25$), $t(41.4) = 2.03$, $p = .0492$; $\Delta M = 0.74 \mu V$ vs. $0.36 \mu V$, respectively.

These findings confirm that painful stimuli evoke an LPP-like response during empathic engagement, with enhanced neural activity in anxious individuals. Anxiety may heighten affective sensitivity and attentional allocation to others' suffering. Small effect sizes suggest additional factors may modulate this response and merit further investigation.



Disclosures: L.V. Sánchez-Vincitore: None. M.E. Castello: None. J. Duñabeitia: None. F. Romero: None. F. Moreira: None. H. Marte-Santana: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.17/Web Only

Topic: H.06. Anxiety Disorders

Support: FIG Grant IITR/SRIC/2741

Title: Investigating the effect of 4-7-8 breathing technique in cynophobia

Authors: *V. MAITHANI¹, D. SINGH², R. CHAHAR⁴, M. K. ASTHANA³;

¹Humanities and Social Sci., Indian Inst. of Technology, Roorkee, Roorkee, India; ²Humanities and Social Sci., ³Dept. of Humanities & Social Sci., Indian Inst. of Technol. Roorkee, Roorkee, India; ⁴The Ctr. for Psychology, Univ. of Hyderabad, Hyderabad, India

Abstract: Cynophobia refers to the irrational fear of dogs that can elicit fearful emotional and physiological responses. The current study investigates the effects of the 4-7-8 deep breathing technique on the participants who fear dogs, known as cynophobia. Twenty-eight participants were screened based on the Fear of Dogs questionnaire. The participants were randomly divided into groups of Deep-breathing (DB: N=14, Mean age=23.50, SD=3.63) and No-deep-breathing (NDB: N=14, Mean age=20.93, SD=2.76). In the deep-breathing group, participants were instructed to practice inhaling for 4 seconds, holding their breath for 7 seconds and exhaling for 8 seconds while viewing the stimuli presentation. The No-deep-breathing group was not given any such instructions. The experimenter selected four images of dogs and four neutral animals

from the IAPS database. A total of 36 trials were presented to the participants in the experiment. The experimenter recorded participants' pre- and post-valence, arousal and dominance ratings. Both groups were presented with anticipatory cues (blue, red or green circles) followed by the dog, blank screen or neutral animal images, each image repeated 3 times, and the blank screen repeated 12 times. Each trial presentation followed a fixation of 15 seconds. An independent sample t-test indicated a non-significant difference between the two groups regarding the dog stimuli's valence, arousal, and dominance. Although significant differences were not subjectively observed for the threatening stimuli (dog), electrophysiological data suggest a change during the anticipation of the threat stimuli. EEG data from the eight frontocentral scalp electrodes indicated an ERP signal, i.e. Late positive potential (LPP), while anticipating emotional stimuli. The independent sample t-test for LPP reflected a trend towards significant difference ($t(23) = -2.06, p = 0.051$) for the anticipation of dog cues between the DB group and the NDB group. The results suggest that the deep breathing technique might have modulated the emotional reactivity towards anticipating the threatening stimuli (dog), indicating that it may influence anticipatory emotional processing not observed in self-report measures.

Disclosures: V. Maithani: None. D. Singh: None. R. Chahar: None. M.K. Asthana: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.18/X14

Topic: H.08. Drugs of Abuse and Addiction

Support: Marian University Intramural SLC Grant
Marian University Intramural Professional Development Grant

Title: The influence of narcissistic traits on the reinforcement value of family across different patterns of alcohol use

Authors: H. R. REUTER, J. KELLOGG, *S. L. WOLFMAN;
Psychological Sci. and Counseling, Marian Univ., Indianapolis, IN

Abstract: Alcohol use disorder (AUD) is a complex psychiatric condition influenced by a variety of factors, including dysfunctional reward processing, family dynamics, and personality traits. AUD often disrupts relationships, and the behavioral economic and family systems frameworks suggest that family and alcohol use serve as a competing reinforcers. Additionally, individuals with high narcissism may find familial support less reinforcing. This study examines the relationship between narcissism, alcohol use, and the reinforcement value of family. Adult alcohol users completed an online survey assessing problematic alcohol use, narcissistic traits, and the reinforcing value of family activities, using the Alcohol Use Disorders Identification Test, Pathological Narcissism Inventory, and a modified Adolescent Reinforcement Survey Schedule, respectively. Results indicate that narcissism and problematic alcohol use are

positively correlated, and that both are negatively correlated with reinforcement value of family. These findings highlight the potential role of narcissism in diminishing the reinforcing value of family engagement among alcohol users and underscore the importance of addressing personality factors in substance use interventions.

Disclosures: H.R. Reuter: None. J. Kellogg: None. S.L. Wolfman: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.19/X15

Topic: H.04. Emotion

Support: RF1AG061355
NICHHD/NIH K08HD107161
NIH-NHLBI R21HL170255

Title: Menstrual Cycle Influences the Neurophysiology of Sleep-Linked Mood Variability

Authors: *P. T. UZOIGWE¹, A. SHUSTER², A. MOREHOUSE², N. SATTARI^{3,2}, K. C. SIMON², F. C. BAKER⁴, S. MEDNICK⁵;

¹Cognitive Neurosci., Univ. of California, Irvine, IRVINE, CA; ²Univ. of California, Irvine, Irvine, CA; ³UCR, Riverside, CA; ⁴Ctr. for Hlth. Sci., SRI Intl., Menlo Park, CA; ⁵Univ. of California Irvine, Irvine, CA

Abstract: Sleep and mood are known to be interrelated, yet little is known about how their interaction is shaped by underlying brain physiology across the menstrual cycle. Prior work often overlooks phase-specific neurobiological modulation and lacks sufficient sample sizes or within-subject designs. This study examines how menstrual cycle phases influence the relationship between sleep neurophysiology and mood regulation. Fifty-nine healthy women (ages 18-35) with regular menstrual cycles were studied over two cycles using a within-subject, phase-confirmed design. Participants underwent four in-lab overnight polysomnography (PSG) sessions (32-channel EEG) during the menses (MS), late follicular (LF), mid-luteal (ML), and late-luteal (LL) phases. Daily mood was assessed before and after sleep, and salivary hormone levels were collected. Pearson correlations and mixed-effects models were used to evaluate how neurophysiological sleep metrics (REM, N1, SWS, total sleep time [TST], and wake after sleep onset [WASO]) predicted next-day mood changes across phases. Multiple comparisons were corrected using the Benjamini-Hochberg procedure. Results showed that mood-sleep relationships varied by menstrual cycle phase. Greater WASO was associated with increased anger and frustration. REM and SWS, reflecting distinct neurophysiological sleep states, were linked to improved positive mood, particularly during MS and LL phases. Positive mood improvements tied to SWS differed significantly between LL vs. LF and LF vs. ML phases (adjusted $p < 0.05$). For anger, REM-related effects varied across LF, ML, and LL phases, while

SWS effects differed between MS and LL. N1 sleep also showed phase-specific associations with mood. Across phases, more N2 and longer TST predicted reduced negative mood. These findings demonstrate that neurophysiological sleep stages influence mood variability in a menstrual-phase-dependent manner. Our results underscore the importance of incorporating sleep measures and hormonal status in studies of mood regulation, offering a more nuanced understanding of female affective neuroscience.

Disclosures: P.T. Uzoigwe: None. A. Shuster: None. A. Morehouse: None. N. Sattari: None. K.C. Simon: None. F.C. Baker: None. S. Mednick: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.20/X16

Topic: H.08. Drugs of Abuse and Addiction

Support: VA Grant IK2 CX001584
VA Grant 1I01CX002456

Title: Does Trauma-Focused Psychotherapy Shift Reward Processing in Individuals with Depression: A Moderating Role of Alcohol Craving

Authors: *S. H. NORTHUP¹, E. MEHTA², D. N. DUN⁴, S. NORMAN⁵, A. SIMMONS⁶, A. D. SPADONI⁷, K. M. HARLE³;

¹San Diego Veterans Med. Res. Fndn., ³Dept. of Psychiatry, ²VA San Diego Healthcare Syst., San Diego, CA; ⁴Res., San Diego VA Healthcare Syst., Folsom, CA; ⁵Psychiatry, UCSD, San Diego, CA; ⁶Psychiatry, UCSD, La Jolla, CA; ⁷UCSD, San Diego, CA

Abstract: Maladaptive alcohol use frequently co-occurs with depression and traumatic stress disorders, contributing to poorer treatment outcomes. Importantly, all three conditions have been linked to impairments in reward processing, including disruptions in reward learning and decision-making. However, it remains unclear whether such mechanisms can improve following treatment and whether alcohol craving, which reflects a shift in reward sensitivity towards maladaptive alcohol use, plays a role. To bridge this gap, we used a reinforcement learning framework to examine how baseline alcohol craving influences changes in reward sensitivity following evidence-based treatment.

Trauma exposed veterans (N = 51, 89.8% male, ages 29-60) with at least mild depression (Patient Health Questionnaire-9 >10) completed a multi-armed bandit task at the beginning and end of trauma-focused psychotherapy. In the task, they had to choose between different options with unknown reward rates with the goal of maximizing points. A Rescorla-Wagner model was fit for participant decisions to extract parameters of reward learning and decision making. Self-reported alcohol craving was assessed at baseline using the Desires for Alcohol Questionnaire (DAQ-28).

Participants showed an increase in a model parameter associated with reward maximization following treatment ($F(1, 114.96) = 30.64, p < .001$). Baseline DAQ further moderated this effect ($F(3, 115) = 6.25, p < .001$). Specifically, those endorsing lower craving (DAQ < 35) had significantly greater increases in the reward maximization parameter compared ($t(119) = 2.972, p = 0.03$), which was not apparent for those with higher craving. Baseline DAQ also moderated treatment-related change in a learning rate parameter ($F(3, 117.8) = 3.76, p = .013$), i.e., those with higher craving (DAQ > 61) exhibiting an increase in this parameter ($t(116.5) = -3.01, p = .06$) to levels similar to low-craving participants.

Baseline alcohol craving moderated changes in reward-based decision-making following evidence-based trauma therapy. Those with minimal alcohol craving may show improvement in the drive to maximize healthy reward. Those with higher cravings had the lowest baseline learning rates but improved significantly, reflecting a more normative level of reward prediction updating. These findings support the use of reinforcement learning paradigms to identify treatment-relevant subtypes in trauma-exposed individuals.

Disclosures: S.H. Northup: None. E. Mehta: None. D.N. Dun: None. A. Simmons: None. A.D. Spadoni: None. K.M. Harle: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.21/Y1

Topic: H.06. Anxiety Disorders

Title: Using Data-Driven Techniques for Capturing Anxious Arousal With Movie fMRI

Authors: *P. QAMAR¹, J. LENTZ², D. S. PINE¹, P. KIRK¹;

¹Section on Develop. and Affective Neurosci., Natl. Inst. of Mental Hlth., Bethesda, MD; ²NIH, Bethesda, MD

Abstract: Clinical neuroscience has traditionally used task paradigms or resting-state to understand the pathophysiology of anxiety disorders. An emerging alternative uses movie fMRI, which boosts phenotype prediction and offers a platform for understanding ecologically rich experiences. While the complexity of movie stimuli confers many advantages, no standard analytic pipeline exists. We explored the sensitivity of a frequency-domain measure of the fMRI signal, global mean normalized amplitude of low-frequency fluctuations (mALFF), in capturing arousal during anxiogenic movies. We hypothesized mALFF during an anxiogenic movie would correlate with anxiety ratings in anxiety-relevant brain structures, including positively with the subcortex and salience network, and negatively with the default mode network.

We used openly available data from the California Institute of Technology Conte Center dataset. 58 healthy adults completed structural and functional MRI scanning. Participants watched an 8-minute anxiogenic clip of “Bang! You’re Dead (1954)” and a 5-minute non-anxiogenic clip of “Partly Cloudy”. Participants self-reported trait anxiety via the State Trait Anxiety Inventory. In

AFNI, voxel-wise mALFF measures were calculated per condition and submitted to t-tests. Cluster-correction was applied through a permutation-based approach (voxel threshold: $p < .001$; two-tailed family-wise error corrected results: $p < .05$). Activity was increased across bilateral temporal lobes, dorsomedial prefrontal cortex (dmPFC), and decreased in visual cortex. Exploratory analyses revealed no associations with trait anxiety. To our knowledge, this is the first study that leverages frequency-domain analyses applied to movie fMRI data. mALFF appears to be sensitive to differences in features between the movies. We suggest brain activity measures may represent movie-related differences in language processing in temporal lobes, visual information in occipital lobes, and ‘higher-order’ socio-emotional processing (dmPFC). Specifically, increased low frequency power observed in dmPFC may relate to threat processing during the anxiogenic movie condition. In sum, this study highlights mALFF as a potentially clinically insightful, data-driven technique for capturing movie-evoked brain activity with fMRI.

Disclosures: P. Qamar: None. J. Lentz: None. D.S. Pine: None. P. Kirk: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.22/Y2

Topic: G.03. Stress and the Brain

Title: Social affective vulnerability: the interplay of social stress, childhood trauma, and brain volume

Authors: *O. BERHE^{1,2}, M. REICHERT^{1,2,3,4}, A. S. MEYER-LINDENBERG^{1,2}, H. TOST^{1,2}; ¹Central Inst. of Mental Hlth., Mannheim, Germany; ²Partner site Mannheim, German Ctr. for Mental Hlth. (DZPG), Mannheim, Germany; ³Dept. of Sport and Sport Science, mental mHealth Lab., Karlsruhe Inst. of Technol., Karlsruhe, Germany; ⁴Dept. of eHealth and Sports Analytics, Ruhr-University Bochum, Bochum, Germany

Abstract: Aversive social experiences critically shape affective well-being, especially among individuals exposed to childhood trauma (Monninger et al., 2023; Berhe et al., 2023). Yet, a detailed understanding of how early-life adversity shapes moment-to-moment social-affective dynamics and their neural correlates in real-world contexts remains limited. Here, we applied social phenotyping capturing interpersonal dynamics via smartphone-based ecological momentary assessment—to a community-based cohort ($n = 349$; 56% female; aged 19-45 years), Participants reported during social interactions about their experience: social dislike (“don’t like company”), preference to be alone (“rather be alone”), and affective valence over one week. These momentary ratings were analyzed using multilevel models to examine within- and between-person associations. Childhood trauma exposure was assessed using the Childhood Trauma Questionnaire. A subsample of 214 participants also underwent 3T structural magnetic resonance imaging (MRI) to examine how stress-regulatory brain regions support these social-

affective experiences. Findings revealed that trauma exposure shapes a stress-prone social-affective style in adulthood: individuals with higher trauma exposure reported greater momentary social aversion ($\beta=0.105$, $p<0.025$) and withdrawal ($\beta=0.152$, $p<0.007$). Daily social stress was linked to smaller hippocampal ($T=4.80$, $p=0.024$), amygdala ($T=3.09$, $p_{FWE}=0.049$), and subgenual ACC volumes ($T=3.77$, $p_{FWE}=0.009$), suggesting stress-sensitive neural adaptations. Importantly, moments of higher social aversion/withdrawal were linked to lower affective well-being ($\beta=-3.24$, $p<0.001$; $\beta=-3.88$, $p<0.001$), reflecting the dynamic, real-world emotional cost of social aversion - social affective vulnerability. Trauma exposure further amplified this relationship ($\beta=-0.193$, $p<0.024$; $\beta=-0.258$, $p<0.002$), highlighting for maladaptive social-affective profile. By integrating social phenotyping with structural neuroimaging, this study offers a novel, ecologically valid model linking early adversity, social-affective experiences, and stress-regulatory brain circuits. These findings reveal targets for interventions designed to address social-affective vulnerability in this vulnerable population.

Disclosures: **O. Berhe:** None. **M. Reichert:** None. **A.S. Meyer-Lindenberg:** F. Consulting Fees (e.g., advisory boards); Daimler and Benz Foundation, EPFL Brain Mind Institute, Fondation FondaMental, Hector II Foundation, Invisio, Janssen-Cilag GmbH, Lundbeck A/S, Lundbeckfonden, Lundbeck Neuroscience Foundation, MedinCell, The LOOP Zürich, University Medical Center Utrecht, University of Washington, the Mental Wellbeing Association, von Behring-Röntgen Foundation. Other; Ärztekammer Nordrhein, Caritas, Clarivate, the German Society for Neuroscientific Assessment, Gentner Verlag, the State Medical Association Baden- Württemberg, LWL Bochum, Northwell Health, Ruhr University Bochum, Penn State University, the Society of Biological Psychiatry, the University Prague and Vitos Klinik Rheingau, American Association for the Advancement of Science, the European College of Neuropsychopharmacology, Servier Int., Thieme Verlag. **H. Tost:** None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.23/Y3

Topic: H.06. Anxiety Disorders

Title: Brain signal variability and gene expression profiles underlying anxiety

Authors: ***P. SIGAR**¹, Z. T. GOODMAN³, J. S. NOMI¹, T. BOLT¹, L. Q. UDDIN²;
¹Univ. of California Los Angeles, Los Angeles, CA; ²Univ. of California Los Angeles, California, CA; ³Univ. of California San Diego Med. Ctr., San Diego, CA

Abstract: Anxiety disorder (AD) is among the most common mental health disorders, often emerging in adolescence and persisting into adulthood. Subclinical anxiety—frequent but not clinically diagnosed symptoms—is highly prevalent and can precede formal AD. While brain signal variability (BSV) shows strong predictive value for neuropsychiatric traits, its relationship to anxiety across age groups remains unclear. This study examined how anxiety symptoms relate

to BSV in a large community sample and whether these neural patterns align with gene expression profiles. We used resting-state functional magnetic resonance imaging (fMRI) and postmortem gene expression data to investigate these associations. Neuroimaging data from the Enhanced Nathan Kline Institute Rockland Sample (n = 574, 60% female, ages 8-85) were analyzed. Anxiety was assessed in the sample using the Multidimensional Anxiety Scale for Children (MASC) for youth and the State-Trait Anxiety Inventory-Trait scale (STAI-Trait) for adults. BSV was computed as the root mean square of successive differences (rMSSD) from voxelwise fMRI time series. Ordinary least squares regression tested anxiety-BSV associations in four models. Controlling for linear age, higher anxiety predicted increased BSV in the precentral and postcentral gyri ($z > 3.3$, cluster $p < 0.05$). When quadratic age was added, associations extended to the cingulate, precentral, and postcentral gyri. No significant effects were found in adolescents (n = 117), but in adults and older participants, higher anxiety was robustly associated with increased BSV in sensorimotor and cingulo-opercular regions ($z > 2.3$, cluster $p < 0.05$). Spatial correlation with gene expression data from the Allen Human Brain Atlas (n = 6 donors, ages 24-57) revealed that BSV-anxiety patterns aligned with the expression of genes involved in synaptic signaling, ion transport, and intracellular communication, including SGK3, DNER, MAPK8, and KLRC3. These findings suggest that anxiety in older individuals is associated with altered temporal brain dynamics in specific networks and may reflect molecular mechanisms regulating excitability and plasticity. This work highlights the utility of non-invasive neuroimaging and transcriptomic integration for uncovering mechanisms of anxiety.

Disclosures: P. Sigar: None. Z.T. Goodman: None. J.S. Nomi: None. T. Bolt: None. L.Q. Uddin: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.24/Y4

Topic: H.06. Anxiety Disorders

Support: Foundation for OCD Research

Title: Identification of a deep brain stimulation target in macaques to model obsessive-compulsive disorder circuitry

Authors: *K. HERBERT¹, S. H. FUJIMOTO², S. KARMACHARYA², A. FUJIMOTO³, C. ELORETTE², M. FIGEE², B. E. RUSS⁴, P. H. RUDEBECK²;

¹Mount Sinai Sch. of Med., New York, NY; ³Dept. of Neurosci., ²Icahn Sch. of Med. at Mount Sinai, New York, NY; ⁴Ctr. for Biomed. Imaging and Neuromodulation, Nathan Kline Inst., Orangeburg, NY

Abstract: Deep brain stimulation (DBS) is an emerging therapy for treatment resistant obsessive-compulsive disorder, targeting specific white matter fiber tracts passing through the

anterior limb of the internal capsule (ALIC). Despite its clinical efficacy, the circuit-level mechanisms that drive symptom relief remain unclear, necessitating the use of animal models. We developed a macaque tractography pipeline that identifies an ALIC DBS target whose connectivity profile is aligned with known human OCD response pathways. To achieve this, we acquired diffusion-weighted images from adult rhesus macaques to measure in vivo anatomical connectivity. We then used the National Institute of Mental Health Macaque Template (NMT) atlas to define key regions associated with OCD in the subject's DWI space, focusing on the ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, and subthalamic nucleus. Using probabilistic tractography, we identified white matter projections that originated from these regions and passed through the ALIC. A target was identified as the point of highest confluence of these three tracts in the ALIC. From this target, we generated secondary tracts to verify projections to the regions of interest and compared these to the human tracts. We also quantified inter-subject variability using Euclidean centroid dispersion and laterality indices. In two macaques, our pipeline reliably localized an ALIC location whose projection profile mirrors the human OCD DBS response tract. The target centroid separation between animals was 1.34 mm in the left hemisphere and 3.26 mm in the right hemisphere. White matter projections from these targets yielded laterality indices within ± 0.04 across both subjects, indicating minimal hemispheric bias. These preliminary findings demonstrate that our pipeline can identify and characterize ALIC DBS targets in macaque. It also enables quantification of inter-subject variability which can identify outliers and guide subject selection. By establishing a framework to identify the human OCD DBS response network in macaques, it creates a platform for future in vivo mechanistic experiments. Future work includes translationally relevant neuroimaging, electrophysiology, and postmortem histology to causally probe the OCD network in ways not feasible in humans.

Disclosures: K. Herbert: None. S.H. Fujimoto: None. S. Karmacharya: None. A. Fujimoto: None. C. Elorette: None. M. Figue: None. B.E. Russ: None. P.H. Rudebeck: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.25/Y5

Topic: H.06. Anxiety Disorders

Support: DBT Wellcome Trust IA Fellowship (IA/I/20/2/505204)
IIT Kanpur start-up grant (No. 2019/373)
NARSAD Young Investigator Grant (No. 27649)

Title: Anxious, wandering minds forage poorly: evidence based on EEG biomarkers and stress neuromodulators

Authors: *P. MITRA¹, G. CHAUHAN², A. RAMAKRISHNAN²;

¹Biol. Sci. and Bioengineering, Indian Inst. of Technol. Kanpur, Kanpur, India; ²Biol. Sci. and Bioengineering, Indian Inst. of Technol. Kanpur, Kanpur, India

Abstract: Mental health disorders are a leading global health burden, with anxiety spectrum disorders among the top contributors (Penninx et al. 2021). A core feature of generalized anxiety disorder is persistent worrying a subtype of mind wandering that disrupts attention by shifting between intrusive thoughts (Fell et al. 2023). Sequential patch foraging similarly requires dynamic shifts between exploration and exploitation, engaging cognitive control systems that may be compromised in anxious individuals (Barack et al. 2024). The anterior cingulate cortex (ACC) underlies both domains, ramping activity prior to foraging decisions (Hayden et al. 2013) and acting as a hub in the default mode network during mind-wandering (Christoff et al. 2009). High trait anxiety has been linked to foraging inefficiencies like premature patch leaving (Yonce et al. 2021), possibly due to increased attentional lapses. To test whether early patch leaving is due to mind wandering like tendencies, we examined whether neural markers of mind wandering—mid-frontal theta beta power ratio and phasic P300 amplitude (Son et al. 2019) reflect trait anxiety's impact on foraging. 55 participants performed a virtual patch foraging task (Barack et al. 2024) while EEG, pupil dilation, and stress neuromodulators like salivary cortisol and norepinephrine via salivary alpha-amylase were collected. Trait anxiety was assessed using the STAI-Y2. Bayesian regression showed that higher available reward was associated with increased P300 amplitude ($\beta = 0.02$, 95% CI [0.01, 0.03]) and decreased theta-beta ratio ($\beta = -0.12$, 95% CI [-0.16, -0.08]), indicating greater engagement when reward availability was high. However, high trait anxiety was linked to elevated baseline theta-beta ratio ($\beta = 1.57$, 95% CI [1.43, 1.71]) and reduced P300 amplitude ($\beta = -0.04$, 95% CI [-0.06, -0.02]), indicating reduced engagement controlling for reward magnitude. Further, moderation-mediation analyses revealed that trait anxiety interacted with cortisol and sAA to alter theta beta ratio (sAA: -0.13 ± 0.02 , $p \leq 0.001$; cortisol: -0.02 ± 0.01 , $p \leq 0.085$) and P300 amplitude (sAA: 0.14 ± 0.02 , $p \leq 0.001$; cortisol: 0.01 ± 0.01 , $p \leq 0.163$). Lastly, trait anxiety and the stress neuromodulators' impact on reward seeking was mediated by both theta-beta and P300 significantly ($p \leq 0.001$). These findings suggest that trait anxiety via stress neuromodulators, promotes mind wandering like neural states that impair adaptive foraging. Future work will test whether enhancing top down control via transcranial alternating current stimulation over dorsolateral prefrontal cortex can reduce over-exploration and mind-wandering during foraging.

Disclosures: P. Mitra: None. G. Chauhan: None. A. Ramakrishnan: None.

Poster

PSTR036: Human and Nonhuman Primate Studies of Emotion and Motivation

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR036.26/Y6

Topic: I.04. Executive Functions

Support: AMED Brain/MINDS Beyond Program (Grant Number: JP18dm0307002) and the JSPS KAKENHI Grants (Grant Numbers 19K03309, 22H01090, 23K22361, 24K21493, and 25K00879)
JST SPRING, Grant Number JPMJSP2109

Title: Altered Resting-State Functional Connectivity Underlying Executive Function in Obsessive-Compulsive Disorder

Authors: *N. AXIMU^{1,2}, S. ZHAHARA^{4,2}, Y. ISOBE², Y. IKEMIZU², E. SHIMIZU⁵, Y. HIRANO³;

¹division of frontier medicine and pharmacy, ³Res. Ctr. for Child Mental Develop., ²Chiba Univ., Chiba, Japan; ⁴Osaka Univ., Osaka, Japan; ⁵Chiba Univ. Grad Sch. Med., Chiba, Japan

Abstract: Obsessive-compulsive disorder (OCD) is a frequently occurring, long-lasting disorder characterized by significant impairment, with a typical lifetime prevalence of 2.3%. Numerous studies have shown abnormalities in prefrontal-striatal circuits in OCD, which support executive function. Therefore, this study used resting-state functional connectivity (rsFC) in OCD patients and healthy controls (HCs) to identify factors associated with executive function, as assessed by the Rey-Osterrieth Complex Figure Test (ROCF), Trail-making test (TMT) and Wisconsin Card Sorting Test (WCST). Twenty OCD patients and 36 healthy controls (HCs) were evaluated for executive function. Both groups underwent functional magnetic resonance imaging (fMRI). We identified rsFC, showing the difference between OCD and HCs using multi-voxel pattern analysis (MVPA) and correlations between neuropsychological scores and their rsFCs in OCD. Results showed that individuals with OCD have lower Copy Presence and Accuracy (CPA) and Delayed Presence and Accuracy (DPA) subscores of the ROCF than HCs; patients with OCD have fewer TMT-B errors than HCs. MVPA-based rsFC analysis revealed that left Postcentral gyrus (PostCG) to right frontal pole (FP), subgenual anterior cingulate cortex (sACC) to right cerebellum2, and sACC to the left superior gyrus (SFG) were stronger, and left PostCG to the right posterior cingulate cortex (PCC) rsFC were weaker in patients with OCD. Moreover, sACC-left SFG connectivity was positively correlated with CPA scores, whereas sACC-right cerebellar Crus II connectivity was positively correlated with organization (ROCF ORG) score in the OCD. Thus, patients with OCD have impaired executive function, which is associated with symptom severity. Excessive resting-state connectivity in sACC-Crus II may be an imaging marker of OCD. Our results identify the neural mechanisms behind the pathophysiology of OCD.

Disclosures: N. Aximu: None. S. Zhahara: None. Y. Isobe: None. Y. Ikemizu: None. E. Shimizu: None. Y. Hirano: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.01/Y7

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA F32 AA029866
NIAAA R01 AA028406
NIAAA L40 AA030427

Title: Increased alcohol-seeking in offspring with prenatal alcohol and cannabinoid co-exposure is associated with sex-specific corticostriatal transcriptomic signatures.

Authors: *S. ROUZER¹, R. C. MIRANDA²;

¹Neurosci. & Exptl. Therapeut., Texas A&M Col. of Med., Bryan, TX; ²Neurosci. and Exptl. Therapeut., Texas A&M Univ., Bryan, TX

Abstract: Background: Alcohol and cannabinoids are two of the most consumed psychoactive substances by pregnant individuals today. Independently, both forms of prenatal exposure have been associated with changes in offspring corticostriatal synaptic activity, as well as increases in drug-seeking behavior. Recently, our lab determined that prenatal co-exposure to alcohol and synthetic cannabinoid CP-55940 increased ethanol self-administration in adult offspring compared to single-drug exposures and drug-free controls. However, it is yet unknown whether these exposure-induced changes in alcohol-seeking are associated with distinct corticostriatal transcriptomic signatures.

Methods: Pregnant C57Bl/6J dams received one of four daily treatments on gestational days 12-15: room air + vehicle (CON), ethanol vapor + vehicle (ALC), room air + CP-55940 (CB; 0.75 mg/kg i.p.), or ethanol vapor + CP-55940 (ALC+CB). Adult male and female offspring completed operant ethanol self-administration before microdissection of the medial prefrontal cortex (mPFC) and dorsomedial striatum (DMS) ($n = 5-8/\text{sex/exposure}$). Independent weighted gene co-expression networks were constructed for each region, and cross-regional eigengene pairs (mPFC-DMS) were regressed against within-subject ethanol intake to obtain adjusted R^2 values and permutation-derived p -values for every exposure/sex cohort.

Results: In males, corticostriatal predictors of alcohol consumption were only present in ALC+CB offspring (MEgreenyellow $\times$ MEblack; $R^2_{\text{adj}} = 0.999$, $p < 0.001$). In females, significant network predictors were present for all groups, but the identity of predictor modules differed by exposure: CON (MEbrown4 $\times$ MEgreenyellow, $R^2_{\text{adj}} = 0.944$, $p = 0.003$), ALC (MEsalmon $\times$ MEpurple, $R^2_{\text{adj}} = 0.996$, $p = 0.004$), CB (MEturquoise $\times$ MEbrown, $R^2_{\text{adj}} = 0.825$, $p = 0.013$), and ALC+CB (MEviolet $\times$ MEMagenta, $R^2_{\text{adj}} = 1.000$, $p < 0.001$). Thus, ALC+CB co-exposure produced a male-specific emergence of alcohol-predicting genes, while females experienced reorganization of existing network predictors.

Conclusions: Gestational alcohol and cannabinoid exposures remodel corticostriatal transcriptomic architecture in a sex- and exposure-dependent manner that dictates the strength and identity of networks predicting voluntary ethanol intake. Therapeutics targeting corticostriatal pathways may therefore require tailoring to an individual's prenatal substance history and biological sex to achieve maximal efficacy against alcohol use disorder.

Disclosures: S. Rouzer: None. R.C. Miranda: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.02/Y8

Topic: H.08. Drugs of Abuse and Addiction

Support: F32AA031396
P50AA017823
R01AA029403
R01AA031472
Republic of Türkiye Ministry of National Education Scholarship
Pennsylvania State University The Huck Institutes of the Life Sciences
Endowment Funds

Title: Adolescent alcohol consumption disrupts adult prefrontal somatostatin functioning and aversion-resistant alcohol preference in mice

Authors: *L. R. SEEMILLER¹, A. SICHER¹, H. UNSAL¹, Y. XIE¹, D. BROCKWAY¹, K. GRIFFITH¹, M. HOSSAIN², P. J. DREW³, N. ZHANG¹, N. A. CROWLEY⁴;

²Dept. of Biomed. Engin., ¹Penn State Univ., University Park, PA; ³Penn State Univ., State College, PA; ⁴Dept. of Biol., Penn State Univ., University Park, PA

Abstract: Alcohol exposure disrupts the normal function of inhibitory somatostatin (SST) neurons, particularly within cortical regions. Changes in cortical SST are likely to be involved in the heightened risk of psychiatric disorders seen with chronic alcohol use. Here, we examined SST cell and peptide functioning and related behavioral outcomes after adolescent binge-like drinking. Male and female C57BL/6J and SST-Cre:Ai32 mice consumed alcohol or water in a drinking-in-the-dark (DID) paradigm throughout adolescence (PND 29-54) and were tested for brain SST or behavior changes 30 days after cessation of DID. Generalized linear modeling (GLM) was used to examine the influence of sex and total alcohol consumed on dependent measures while accounting for cohort and litter effects. Prior experiments from our lab found that prelimbic (PL) SST neurons exhibited increased intrinsic excitability after adolescent alcohol consumption. To examine the functional consequences of this PL SST hyperexcitability, we measured the paired pulse ratio (PPR) of SST optogenetic-evoked inhibitory currents onto pyramidal cells, which was reduced after adolescent alcohol consumption (n=10-11, p=0.04). This suggested stronger SST cell-mediated GABAergic outputs to pyramidal cells. We also found that optogenetic-evoked SST peptide release from SST cells was increased in extracellular aCSF of alcohol-exposed mice (n=8-9, p=0.04). Intriguingly, we found that adult females, and not males, exhibited aversion-resistant alcohol consumption after adolescent alcohol exposure (n=9-11, p=0.04), and this may be related to sex-specific changes in functional connectivity and baseline sex differences in the SST system. We hypothesize that observed behavioral and prefrontal connectivity changes were driven in part via disruption of prelimbic SST signaling. Future work will examine female vulnerability to alcohol and the roles of female-specific variables such as hormonal contraceptives.

Disclosures: L.R. Seemiller: None. A. Sicher: None. H. Unsal: None. Y. Xie: None. D. Brockway: None. K. Griffith: None. M. Hossain: None. P.J. Drew: None. N. Zhang: None. N.A. Crowley: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.03/Y9

Topic: H.08. Drugs of Abuse and Addiction

Support: R00AA029726
R01AA013983

Title: Role of lateral hypothalamic neurons projecting to the lateral habenula in alcohol aversion

Authors: *J. A. BABB, S. BONAUTO, O. BRUNKE, D. DUNLOP, M. M. WEERA;
Tufts Univ., Medford, MA

Abstract: Both avoidance stress coping and blunted sensitivity to the aversive effects of alcohol are known to facilitate increased alcohol drinking, but the relationship between avoidant coping and alcohol sensitivity is unclear. In rats, exposure to predator odor stress produces avoidance behavior in some animals (termed Avoiders) but not all (termed Non-Avoiders). We recently reported that only male Avoiders escalate their alcohol intake (in a free-choice paradigm) after stress, and that greater avoidance behavior also predicted greater aversion-resistant alcohol drinking (Bonauto et al, 2025). We have also found that Avoider rats of both sexes exhibit less alcohol-induced conditioned taste aversion than Non-Avoiders, which suggests that they are less sensitive to the inherent aversive properties of alcohol. To elucidate the neurobiological mechanisms behind this phenomenon, the current study tested the hypothesis that the lateral hypothalamus (LH) to lateral habenula (LHb) circuit is important for mediating the aversive effects of alcohol, and that dysregulation of this circuit contributes to blunted alcohol aversion in Avoiders after stress. Using a combination of in vivo calcium imaging and retrograde tracing approaches, we found that recruitment of LH-LHb neurons following injection of an aversive dose of alcohol was blunted in male Avoider rats compared to male Non-Avoiders and Control rats. Collectively, these data suggest that the stress-induced escalation of alcohol drinking seen in Avoider rats may be facilitated by lower sensitivity to the aversive effects of alcohol.

Disclosures: J.A. Babb: None. S. Bonauto: None. O. Brunke: None. D. Dunlop: None. M.M. Weera: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.04/Y10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH T32AG076455
National Institute on Drug Abuse (DA060335)
Huck Institutes—High Field Magnetic Resonance Imaging Core Facility
(RRID:SCR_024461) for using their Bruker Biospec 70/30.

Title: Sex shapes the neurobiological consequences of chronic alcohol use: Structural, cellular, and functional changes across the Hippobellum network

Authors: *M. C. MARRERO^{1,3}, H. WNUK², H. M. KAMENS⁴, K. H. WANG¹, T. AREFIN^{1,3};
¹Neurosci., ²Biol., Univ. of Rochester Med. Ctr., Rochester, NY; ³Ctr. for Advanced Brain Imaging & Neurophysiol., Rochester, NY; ⁴Biobehavioral Hlth., Penn State Univ., University Park, PA

Abstract: Alcohol use disorder (AUD) affects approximately 3.7% of the global population and contributes significantly to alcohol-related mortality, accounting for nearly 13% of AUD-associated deaths worldwide. At the neurobiological level, alcohol acts as a complex agent that alters multiple molecular pathways—including those involving glial cells—and leads to widespread changes in brain structure and function, particularly in regions critical for learning and memory. Further, there is some evidence that women are more susceptible to alcohol-induced brain changes; however, the cellular and molecular crosstalk on sex-divergent behavioral traits remains understudied. Hence, we aim to bridge this gap using a mouse model of alcohol dependence, combining high-resolution 3D diffusion MRI (dMRI), immunohistochemistry, and behavior. Male and female C57BL/6J (n=40, P60) mice were chronically exposed to alcohol for 7 weeks using an Intermittent 2-Bottle Choice paradigm. dMRI data demonstrated alcohol-induced structural changes in several brain nodes, including the prefrontal cortex, hippocampus (HIP), cerebellum (CB), thalamus (TH), and amygdala, which are tightly interconnected for learning, memory, and higher-order executive functions. We observed significant volume reductions in multiple regions of the TH, HIP, retrosplenial cortex (RSP), and the ansiform cortex of the CB in the alcohol group. Alcohol-induced reduction in fractional anisotropy and axial diffusivity was observed in the HIP (CA1, CA2, entorhinal cortex) and CB regions, indicating weaker white matter integrity in two major hubs of the polysynaptic hippocellum network. Importantly, these changes were more prominent in the female than the male mice. Furthermore, using fiber tractography, we found atypical structural connectivity in the female hippocellum network, specifically between the RSP and HIP. Next, we established a panel of histological markers to assess alcohol-induced changes in myelination, oligodendrocyte precursor cells, and astrocytes in the RSP and CA1. Qualitatively, we see potential alterations to myelination and astrocytes in these two regions, which will be investigated further through ongoing analyses. Our study will provide mechanistic insight into how chronic alcohol abuse influences neuroinflammation and neurodegeneration in the hippocellum network that disturbs cognitive functions in a sex-specific manner.

Disclosures: M.C. Marrero: None. H. Wnuk: None. H.M. Kamens: None. K.H. Wang: None. T. Arefin: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.05/Y11

Topic: I.04. Executive Functions

NIAAA R00-AA025393

NIAAA R21-AA030862

NIAAA R01-AA031452

Title: Chronic alcohol exposure impairs mu-opioid receptor control of behavioral flexibility

Authors: *J. L. JAMES-ROLLINS, L. A. NATIVIDAD;

Col. of Pharmacy, Div. of Pharmacol. and Toxicology, The Univ. of Texas at Austin, Austin, TX

Abstract: Prolonged alcohol misuse induces neuroadaptations in the brain that contribute to the development of addiction. Early dysregulation of limbic circuitry disrupts motivation and emotional processing, which remain key targets in treatment. Naltrexone (NTX), a non-selective opioid receptor antagonist, is often used to reduce heavy drinking and craving; however, it does not reliably improve cognitive function and has poor adherence due to its limited impact on well-being. We previously showed that chronic intermittent ethanol (CIE) vapor exposure in rats impairs cognitive flexibility during abstinence, an effect unaltered by NTX. NTX also increased the number of omitted responses in a set-shifting task, suggesting reduced task engagement. Prior proteomic work from our lab identified reduced phosphorylation of mu-opioid receptors (MORs) in the medial prefrontal cortex (mPFC) of cognitively impaired animals, suggesting altered MOR signaling may contribute to these deficits. Here, we directly examined the role of mPFC MORs in an operant strategy set-shifting task. Male Long-Evans rats underwent 6 weeks of CIE exposure (14 h/day; BAL= 259.9±96.6 mg/dL) or remained ethanol-naïve, followed by implantation of bilateral guide cannulas targeting the mPFC. During abstinence, rats were trained to respond according to a visual cue rule, in which an overhead light signaled the rewarded lever. On abstinence days 10-14, rats received intra-mPFC infusions of CTAP (MOR antagonist), DAMGO (MOR agonist), or vehicle (n= 9-11/group), followed by a shift to a spatial rule in which reward was based on a fixed lever location, independent of the cue. In ethanol-naïve rats, CTAP improved flexibility by facilitating faster rule shifts, whereas DAMGO impaired performance. In contrast, CIE-exposed rats showed no behavioral response to either compound. MOR manipulation also did not alter omissions in either group. The findings demonstrate that MORs support mPFC-dependent cognitive flexibility under normal conditions but lose functional influence following chronic alcohol exposure. While systemic antagonists like NTX may reduce drinking, they appear insufficient to restore executive function and may diminish engagement with cognitively demanding treatments. This highlights the need for adjunctive strategies that target cortical opioid signaling to support abstinence and recovery.

Disclosures: J.L. James-Rollins: None. L.A. Natividad: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.06/Y12

Topic: H.08. Drugs of Abuse and Addiction

Support: MnDrive Postdoctoral Fellowship in Neuromodulation Research
NIH/NIAAA R01AA028770
University of Minnesota Center for Neural Circuits in Addiction Pilot Grant
NIH/NIDA T32DA007234-37

Title: Characterization of paraventricular nucleus of the thalamus projections to the nucleus accumbens in aversion-resistant alcohol drinking

Authors: *M. BAUER, J. MAYER, P. REMDE, B. NEWELL, J. M. RICHARD;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Drinking alcohol despite negative consequences is a defining feature of alcohol use disorder and reward predicting cues can invigorate addiction like behaviors. The nucleus accumbens (NAc) is a brain region that encodes cue learning and is necessary for aversion-resistant alcohol drinking (ARD). The paraventricular nucleus of the thalamus (PVT) and centro-medial thalamus (CM) are thalamic subregions that project into the NAc and may have opposing roles in processing the motivational value of cues whereby PVT-to-NAc neurons silence across learning for reward predicting cues and CM neurons are activated by salient stimuli which alters NAc neural activity. Thus, we hypothesized that activation of PVT-to-NAc neurons would reduce ARD while CM-to-NAc activation would promote ARD. The purpose of this project was to develop a model of ARD with cues and identify the role of PVT-NAc and CM-NAc pathways in ARD. Long-Evans rats trained on a task where one cue predicts the availability of a 0.06 ml alcohol reward, and a different cue predicts nothing. When rats demonstrated successful reward seeking and cue discrimination, they were tested for ARD in the presence of cues. ARD, as measured by comparing alcohol consumption with varying concentrations of quinine-adulterated alcohol (QuA), a bitter tasting compound. ARD was elicited at low concentrations (30, 60, and 90 mg/L) but not at 180 mg/L. We then chemogenetically excited PVT- or CM-to-NAc pathways during ARD. We found a trend toward a significant interaction of pathway and ligand on QuA reward port entries ($p = 0.08$) whereby PVT-to-NAc neural activation trends towards less, while CM-to-NAc neural activation trends towards more reward port entries for QuA. We are currently collecting more data to increase our group sizes. These data suggest that ARD can be elicited under specific parameters and that both the PVT-to-NAc and CM-to-NAc pathways may be involved in this behavior. Additionally, to identify collaterals from PVT-to-NAc neurons we used a cre-dependent synaptophysin virus tracing method and polyethylene glycol-associated

solvent system (PEGASOS) to clear the traced brain. Whole brains were imaged and aligned to the rat brain atlas and collaterals were visually identified. We found PVT-to-NAc projections collateralize in the cingulate, dorsomedial striatum, ventral hippocampus, periaqueductal grey, and zona incerta. A more in-depth analysis on quantification of collaterals in this pathway are underway. Together, these data begin to characterize PVT-to-NAc pathway collaterals and this pathway's role in aversion-resistant alcohol drinking.

Disclosures: M. Bauer: None. J. Mayer: None. P. Remde: None. B. Newell: None. J.M. Richard: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.07/Y13

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH-NIAAA Grant R01AA028770
NIH-NIAAA Grant F31AA031877

Title: Effects of ventral tegmental area dopamine neuron inhibition on stress-induced reinstatement

Authors: *J. AGUIRRE¹, T. TRAN², P. REMDE², P. AZUAJE², J. M. RICHARD²;
¹Dept. of Pharmacol., ²Dept. of Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Stress is a major contributor to relapse in alcohol use disorder, which can occur even after long periods of abstinence. Ventral tegmental area (VTA) Dopamine (DA) neurons have been shown to mediate various forms of relapse to drug-seeking, including stress-induced reinstatement. Yet, even though stress is known to increase alcohol-related behaviors, the role of VTA DA neurons in stress-induced reinstatement of alcohol-seeking remains unclear. Therefore, here we examined the impact of inhibiting VTA DA neurons on alcohol self-administration and during kappa opioid receptor agonist (KOP) stress-evoked reinstatement using a chemogenetic approach in TH-Cre transgenic Long Evans rats. Following 3 weeks of homecage alcohol exposure, rats underwent self-administration training with active lever presses resulting in the delivery of 15% EtOH paired with a visual and auditory cue, while inactive lever presses had no consequences. Following training, rats underwent surgery for cre-dependent expression of an hM4Di virus or mCherry control. Counterbalanced DREADD ligand DCZ (0.1 mg/kg) or vehicle injections were given prior to testing under extinction conditions, during stress-induced reinstatement, and during self-administration. We observed a trend toward a significant decrease in lever pressing following DCZ under extinction conditions in VTA DA neuron inhibition rats, but not control animals. Additionally, we saw a significant decrease in lever pressing following DCZ injections in hM4Di rats during self-administration. Using the KOP agonist as the stressor led to a significant increase in the reinstatement of alcohol seeking in hM4Di rats that received

DCZ. In addition, there was a VTA DA inhibition effect seen during the reinstatement test days; hM4Di animals significantly increased their active lever pressing when treated with DCZ compared to saline. Overall, our data suggests that the impact of inhibiting VTA DA neurons may depend on the level of basal alcohol seeking and the current stress state of the animal. Future work is needed to fully understand the role of VTA DA neurons following exposure to a stressor like the KOP agonist that increases alcohol seeking.

Disclosures: J. Aguirre: None. T. Tran: None. P. Remde: None. P. Azuaje: None. J.M. Richard: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.08/Y14

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH Grant T32 AA007456
NIH Grant AA029841
NIH Grant AA029498
NIH Grant AA027700
NIH Grant P60 AA006420
NIH Grant AA017447
NIH Grant AA021491

Title: Post-traumatic stress disorder and alcohol use disorder: Investigating the role of BDNF in the Central Amygdala

Authors: C. ST. ONGE¹, ***B. CRUZ**¹, M. PALMISANO⁴, C. M. ERIKSON¹, A. E. GONZALEZ², J. BENEDICT³, R. VLKOLINSKY⁵, A. WARDEN⁶, R. MAYFIELD⁷;
²Translational Med., ¹The Scripps Res. Inst., San Diego, CA; ³The Scripps Res. Inst., La Jolla, CA; ⁴The Scripps Res. Inst., The Scripps Res. Institute, La Jolla, CA, San Diego, CA; ⁵Basic Sciences, Division of Radiation Res., Scripps Res., La Jolla, CA; ⁶The Univ. of Texas at Austin, Austin, TX; ⁷WCAAR, The Univ. of Texas at Austin, AUSTIN, TX

Abstract: Individuals with post-traumatic stress disorder (PTSD) show high prevalence of alcohol use disorder (AUD), disrupted sleep, and hyperarousal and are at greater risk for enhanced alcohol drinking and relapse. PTSD-AUD are frequently co-occurring, yet mechanistic insights and effective treatments for this comorbidity remain limited. Emerging evidence implicates immune-related pathways as critical regulators of central nervous system homeostasis and dysfunction associated with both PTSD-AUD. In humans, a polymorphism in the brain-derived neurotrophic factor (BDNF) gene is linked to earlier onset and increased severity of alcohol dependence, as well as elevated risk of relapse. Both BDNF and its receptor, tropomyosin receptor kinase B (TrkB), are highly expressed in the central amygdala (CeA), a

key integrative hub for stress and alcohol dependence. Our prior findings indicate that stress and alcohol exposure suppress *Bdnf* gene expression while upregulating the pro-stress neuropeptide corticotropin-releasing factor (CRF; *Crh*). We hypothesized that CeA BDNF dysfunction, exacerbated by hyperactive stress signaling, contributes to the pathophysiology of comorbid PTSD-AUD. To test this hypothesis, we used a multidisciplinary approach including behavioral assessments, electrophysiology, imaging analysis, qPCR, and transcriptome analysis to determine the role of the CeA BDNF pathway in a rodent model of PTSD-AUD. This model incorporated a shock stressor preceded by voluntary alcohol consumption in male and female Wistar rats. Our results revealed significant enrichment of BDNF associated pathways in the CeA between stress- and alcohol-exposed rats compared to controls. Whole-cell patch-clamp recordings of GABAergic miniature inhibitory post-synaptic currents (mIPSCs) demonstrated that exogenous application of BDNF on CeA neurons significantly decreased vesicular GABA release. Pharmacological restoration of BDNF via intra-CeA microinjections prior to alcohol access resulted in reduced alcohol intake. Bulk gene expression across eight brain regions further demonstrated widespread reductions in *Bdnf* and *TrkB* gene expression in stress- and alcohol-exposed rats. Collectively, these findings suggest that the BDNF system is compromised following stress- and alcohol-exposure, which contributes to the pathophysiology of PTSD-AUD comorbidity. Restoration of BDNF-related pathways may represent a promising therapeutic avenue for addressing the intersection of stress and alcohol use.

Disclosures: C. St. Onge: None. B. Cruz: None. M. Palmisano: None. C.M. Erikson: None. A.E. Gonzalez: None. J. Benedict: None. R. Vlkolinsky: None. A. Warden: None. R. Mayfield: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.09/Y15

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIAAA R01 AA026537
NIGMS K12 GM000678

Title: Stress-coping behavior during predator odor exposure is associated with differences in reliance on habitual behavior and motivation for sucrose and alcohol in rats

Authors: *B. N. BENDER¹, M. E. HOFFMAN¹, A. M. MOSERA¹, J. BESHEER²;
¹Bowles Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC;
²Psychiatry; Bowles Ctr. for Alcohol Studies, Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: Post-traumatic stress disorder (PTSD) is a chronic psychiatric disorder that impacts a subset of individuals who experience a traumatic event. PTSD is often comorbid with alcohol

use disorder (AUD). Some symptoms of PTSD and AUD involve altered motivation and over-reliance on automatic, habitual behaviors, and individuals with PTSD and AUD show adaptations in reward- and habit-related brain regions. We use predator odor (2,3,5-Trimethyl-3-Thiazoline, TMT) exposure as a stressor that has been shown to produce PTSD-like symptomology in rats. Our lab has shown that individual differences in stress-coping behaviors such as freezing and defensive digging during TMT exposure can predict long-term differences in alcohol-related behaviors and altered neurobiology, particularly in females. We hypothesized that individual differences in behavior during TMT exposure would predict reliance on habitual reward-seeking (Exp 1), preference for alcohol vs. sweetened solution, and increased motivation for alcohol reward (Exp 2). Adult Long Evans rats were exposed to control or TMT for 10 minutes in a novel cage with bedding, and digging and freezing were quantified to separate rats into groups based on individual differences. In Experiment 1 (n=48, 24 males and females), rats were trained to self-administer a sweetened solution (20% sucrose or maltodextrin with 0.05% Kool-Aid) up to an RR20 (random ratio) reinforcement schedule. Two weeks after TMT exposure, outcome devaluation by specific satiety was used to determine if behavior was habitual. In Experiment 2 (n=24, females) rats were trained to press one lever for sucrose (1-2%) and another lever for alcohol (15%). Preference for alcohol over sucrose was evaluated before and 2 weeks after TMT exposure, and then motivation for competing reinforcers was evaluated with a progressive ratio schedule. In Exp. 1, rats that displayed more defensive digging behavior were more sensitive to outcome devaluation, which suggests increased goal-directed behavior. In Exp. 2, more lever presses for sucrose both before and after TMT were correlated with less digging during TMT exposure, and TMT-exposed rats had increased motivation for both alcohol and sucrose. Overall, these findings suggest that behavior during a stressful experience can predict habitual and motivated behavior for both alcohol and natural rewards, which may help identify individuals at risk for aberrant reward-related behaviors after a traumatic event.

Disclosures: B.N. Bender: None. M.E. Hoffman: None. A.M. Mosera: None. J. Besheer: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.10/Y16

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA R01AA021505
NIAAA R01AA027768
NIAAA U01AA025932

Title: Distinct Glutamatergic and Opioidergic Inputs to the SCN and Their Modulation by Alcohol: Implications for Alcohol Use Disorder

Authors: *W. PURVINES^{1,2}, J. JONES³, J. WANG^{2,4};

¹Texas A&M Univ. Neurosci. Inst. For Neurosci., College Station, TX; ²Dept. of Neurosci. & Exptl. Therapeut., Texas A&M Hlth. Univ. Sci. Ctr., Bryan, TX; ³Biol., ⁴Texas A&M Univ. Neurosci. Inst. For Neurosci., Texas A&M Univ., College Station, TX

Abstract: Alcohol Use Disorder (AUD) is frequently associated with disruptions in circadian rhythms. Although preclinical studies have shown that alcohol affects circadian phase-shifting, its direct impact on the physiology of the suprachiasmatic nucleus (SCN), the brain's master circadian clock, remains poorly understood. Here, we demonstrate that acute ethanol exposure increases the spontaneous firing of SCN neurons. Using cell-attached recordings in SCN slices from adult mice, we found that bath application of ethanol significantly elevated neuronal firing rates. To determine whether this effect involved GABAergic transmission, we applied GABA receptor antagonists. These antagonists also increased SCN firing, confirming that GABA is inhibitory in our preparation and suggesting that ethanol's excitatory effect is not mediated via GABAergic mechanisms. We next examined glutamatergic input from the retinohypothalamic tract (RHT), the SCN's primary excitatory afferent. In VGlut2-Cre;Ai32 mice, optogenetic stimulation of presumed RHT terminals evoked robust, AMPA receptor-dependent excitatory postsynaptic currents (EPSCs) and increased firing in SCN neurons in a reversible manner. Given both the established interaction of alcohol and endogenous opioid systems and the clinical use of the μ -opioid receptor (MOR) antagonist naloxone in AUD, we also investigated the role of MOR-expressing inputs to the SCN. Using MOR-Cre;Ai32 mice revealed that most SCN neurons exhibited reversible excitation in response to optogenetic stimulation of MOR+ fibers, with a smaller subset showing inhibition. These effects were synaptically mediated and blocked by the AMPA receptor antagonist DNQX, indicating that a portion of MOR+ input is glutamatergic. Finally, confocal imaging in MOR-Cre;Ai14 mice confirmed MOR expression in RHT fibers and in a subset of SCN neurons. Collectively, our findings reveal glutamatergic and opioidergic synaptic inputs to the SCN and demonstrate that acute alcohol enhances SCN excitability, potentially through modulation of these excitatory pathways. These insights provide new avenues for understanding circadian dysregulation in AUD.

Disclosures: W. Purvines: None. J. Jones: None. J. Wang: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.11/Z1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA Grant R01AA021505
R01AA027768
U01AA025932

Title: Functionally distinct dMSN ensembles in the dorsomedial striatum encode voluntary alcohol consumption and compulsive alcohol seeking

Authors: *Z. LI¹, T. TAN³, X. XIE⁴, W. WANG⁵, W. PURVINES⁶, B. HENDERSON², J. WANG⁷;

²Neurosci., ¹Texas A&M Univ., College Station, TX; ³Neurosci., Oujiang Lab., Houston, TX; ⁴Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX; ⁵Neurosci. and Exptl. Therapeut., Baylor Col. of Med., Houston, TX; ⁶Texas A&M Univ. Neurosci. Inst. For Neurosci., College Station, TX; ⁷Dept. of Neurosci. & Exptl. Therapeut., Texas A&M Hlth. Univ. Sci. Ctr., Bryan, TX

Abstract: The dorsomedial striatum (DMS) plays a central role in reinforcing addictive behaviors. Direct-pathway medium spiny neurons (dMSNs) within the DMS are particularly implicated in alcohol use disorder (AUD), with prior studies showing enhanced excitatory synaptic transmission in these neurons following chronic alcohol exposure. To dissect the ensemble-specific contributions of dMSNs to alcohol-related behaviors, we utilized triple-transgenic *FosCreER*; *Snap25-EGFP*; *D1tdTomato* mice, in which dMSNs are labeled with tdTomato and activated neurons are permanently tagged with EGFP following 4-hydroxytamoxifen (4-OHT) administration. We found that dMSN ensembles activated during two-bottle choice (2BC) drinking exhibit enhanced cortico-striatal synaptic transmission compared to non-activated dMSNs. Furthermore, ensemble labeling using *ArcCreER* mice revealed that the DMS contained more alcohol-activated neuronal ensembles than other striatal regions. Behaviorally, chemogenetic inhibition of TRAPed dMSN ensembles activated during 2BC significantly suppressed alcohol consumption in a subsequent 2BC session, even when alcohol was adulterated with quinine. However, this manipulation did not affect operant self-administration (OSA) behavior. In contrast, inhibition of OSA-activated dMSN ensembles reduced both alcohol seeking during OSA and subsequent consumption in the 2BC test, independent of quinine adulteration. Two-time-point TRAPing and Arc staining analyses further demonstrated minimal overlap between neuronal ensembles engaged during 2BC and those activated during OSA. Together, these results indicate that voluntary alcohol consumption and compulsive alcohol seeking are mediated by distinct dMSN ensembles within the DMS.

Disclosures: Z. Li: None. T. Tan: None. X. Xie: None. W. Wang: None. W. Purvines: None. B. Henderson: None. J. Wang: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.12/Z2

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA021505
NIH Grant R01AA027768
NIH Grant U01AA025932

Title: Distinct Cell-Type-Specific Striatal Engrams Control Relapse and Extinction of Alcohol-Associated Memories

Authors: *J. WANG¹, X. XIE¹, Y. HUANG¹, R. CHEN¹, Z. HUANG¹, H. GANGAL¹, J. LU¹, A. CRUZ², V. VIERKANT¹, R. J. SMITH²;
¹Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX; ²Dept Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: Alcohol relapse, a major challenge in treating alcohol use disorder, is driven by persistent alcohol-associated memories. Identifying the specific neuronal ensembles that encode these memories is essential for developing targeted relapse-prevention strategies. Here, we revealed a dual-ensemble architecture in the dorsal striatum, where distinct populations of direct-pathway medium-spiny-neurons (dMSNs) encoded opposing alcohol-related memories. A matrix-enriched dMSN population was recruited during operant alcohol self-administration to encode cue-alcohol memories. This ensemble was marked by long-lasting synaptic potentiation between alcohol-activated cortical inputs and recruited dMSNs, and mimicking this synaptic change was sufficient to induce relapse-like behavior. Conversely, extinction engaged a separate, striosome-enriched dMSN population. Functional manipulation confirmed the opposing roles of these ensembles: activating the self-administration ensemble drove operant reinforcement and promoted relapse, whereas activating the extinction ensemble failed to support reinforcement and suppressed relapse. These findings reveal a striatal dual-ensemble system encoding competing alcohol memories and suggest frameworks for targeted relapse prevention.

Disclosures: J. Wang: None. X. Xie: None. Y. Huang: None. R. Chen: None. Z. Huang: None. H. Gangal: None. J. Lu: None. A. Cruz: None. V. Vierkant: None. R.J. Smith: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.13/Z3

Topic: H.08. Drugs of Abuse and Addiction

Support: Leon Levy Foundation

Title: Brain-wide signatures of alcohol withdrawal using two-timepoint activity labeling

Authors: *R. SETARA¹, E. J. KYZAR², M. EISENGART¹, S. VIRKAR¹, L. ROGERSON¹, C. D. SALZMAN¹;
¹Zuckerman Inst., ²Psychiatry, Columbia Univ., New York, NY

Abstract: Gaining insight into the neural processes underlying alcohol withdrawal is essential for developing more effective treatments for alcohol use disorder (AUD). Withdrawal and associated behaviors are likely mediated by large-scale coordination of brain activity. However, widely used methods for measuring neural engagement across the brain—such as single-timepoint cFos immunohistochemistry—often lack sensitivity and are prone to noise and variability. To this end, we employed a recently developed approach—two-timepoint neural activity labeling with subtraction (TTP-S)—to quantify overlapping patterns of neural activation during alcohol withdrawal at distinct timepoints. We applied the TTP-S framework to a cohort of mice exposed to different withdrawal trajectories. One group underwent alcohol withdrawal at both timepoints (withdrawal-withdrawal, WW group; n=5) following two-bottle choice consumption of 10% alcohol or water. A second group experienced withdrawal followed by re-exposure to alcohol (withdrawal-ethanol, WE group; n=5) using the same assay. Our TTP-S procedure enabled us to isolate neural populations consistently engaged during withdrawal, distinguishing them from those activated differentially in withdrawal versus intoxicated states. Compared to cFos staining alone, TTP-S demonstrated higher sensitivity in identifying active neural populations in response to withdrawal. Brain-wide analysis revealed over 100 regions activated at both timepoints during alcohol withdrawal. These included known sites implicated in withdrawal, such as the anterior insula and central nucleus of the amygdala, as well as novel regions like the supramammillary nucleus and dorsomedial hypothalamus. Our design also enabled the identification of brain regions containing separate, intermingled neuronal populations differentially activated in withdrawal versus intoxication (in WE mice), potentially mediating the behavioral switch between these states. These included neuromodulatory structures such as the ventral tegmental area, substantia nigra, and raphe nucleus, as well as the superior colliculus. Additionally, we used DeepLabCut for behavioral phenotyping during withdrawal in the elevated plus maze and open field test, correlating these behavioral measures with whole-brain activation patterns. Together, this approach integrates whole-brain activity mapping with behavioral assays to elucidate how alcohol withdrawal and re-exposure shape motivated behavior through distinct patterns of neural ensemble activation.

Disclosures: R. Setara: None. E.J. Kyzar: None. M. Eisengart: None. S. Virkar: None. L. Rogerson: None. C.D. Salzman: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.14/Z4

Topic: H.08. Drugs of Abuse and Addiction

Support: Leon Levy Foundation

Title: Whole-brain neural activity mediating a long-lasting reversal of alcohol preference

Authors: *E. J. KYZAR¹, R. SETARA¹, M. EISENGART¹, S. VIRKAR¹, L. ROGERSON¹, A. RAMIREZ¹, C. D. SALZMAN²;
²Zuckerman Inst., ¹Columbia Univ., New York, NY

Abstract: The motivation to consume alcohol is a complex process that involves the coordination of activity across many brain regions. Previous studies have focused on a relatively small number of these regions, and behavioral paradigms seeking to understand alcohol-seeking behavior have relied on devaluation procedures that change the qualities of alcohol as a stimulus (e.g., quinine adulteration). Here, we utilize a novel method called two-timepoint labeling with subtraction (TTP-S), which utilizes Trap2: Ai14 mice to label active populations of cells with 4-hydroxytamoxifen (4-OHT; 50mg/kg, i.p.) at timepoint 1, followed by sacrifice and labeling for cFos staining at timepoint 2. In a pilot experiment, we unexpectedly found that 4-OHT resulted in a lasting reversal of alcohol preference. We further explored this effect in C57BL6/J mice and confirmed that a single dose of 4-OHT led to a decrease in alcohol preference that lasted for 1-2 weeks compared to vehicle-treated mice. 4-OHT also led to an avoidance of sucrose in a sucrose preference test, though this effect only persisted for 2-3 days. We hypothesized that aversive effects may be mediating the avoidance seen after 4-OHT-stimulus pairing in mice. To investigate this, we conducted a conditioned taste avoidance (CTA) procedure and found that mice avoided a novel flavor previously paired with 4-OHT treatment. Additionally, 4-OHT caused a conditioned place avoidance (CPA) compared to vehicle-treated compartments. Our TTP-S analysis showed that 59 brain areas showed significant activity during the alcohol preference switch, including the orbitofrontal cortex (OFC), anterior insula, and basolateral amygdala (BLA). We performed circuit tracing and showed that projections to OFC from BLA and claustrum are activated during our alcohol devaluation procedure. Our experiments demonstrate that 4-OHT can be used as a tool to devalue alcohol by pairing its consumption with a negative outcome, creating a lasting decrease in alcohol preference. We uncovered brain regions that mediate alcohol devaluation, which may have translational relevance in exploring areas that process negative consequences associated with alcohol use.

Disclosures: E.J. Kyzar: None. R. Setara: None. M. Eisengart: None. S. Virkar: None. L. Rogerson: None. A. Ramirez: None. C.D. Salzman: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.15/Z5

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 2R01AA023610

Title: Role of transforming growth factor beta receptor 2 in light alcohol consumption induced cerebral angiogenesis

Authors: *P. SUBEDI, U. SUBEDI, H. SUN, J. KOTICHA;
Louisiana State Univ. Hlth. Sci. Ctr. Shreveport, Shreveport, LA

Abstract: Background: Multiple meta-analyses indicate that light alcohol consumption (LAC) not only reduces the incidence of ischemic stroke but also protects the brain against its ischemic damage. In addition, LAC lowers the risk of dementia, which is linked to impaired cerebral blood flow. Recent studies found that LAC promotes cerebral angiogenesis, which is positively associated with survival and better functional recovery following ischemic stroke. Our goal is to investigate the mechanism that accounts for LAC-induced cerebral angiogenesis. **Methods:** In *in vitro* studies, we examined the effect of chronic and acute low-concentration alcohol exposure on the expression of transforming growth factor beta receptor 2 (TGF β R2) in C57BL/6J Mouse Brain Microvascular Endothelial Cells (MBMVECs). In addition, we examined the effect of acute low-concentration alcohol exposure on migration and proliferation of MBMVECs in the presence or absence of TA-02 (a selective antagonist of TGF β R2) and LY2109761 (a selective antagonist of both TGF β R2 and TGF β R1). In *in vivo* studies, we examined the effect of LAC on the expression of TGF β R2 and phosphorylated TGF β RI (pTGF β RI) in the cerebral cortex of C57BL/6J mice. Furthermore, we evaluated the influence of TA-02 and LY2109761 on LAC-induced cerebral angiogenesis under basal conditions and following ischemic stroke. **Results:** Chronic and acute low-concentration alcohol exposure increased TGF β R2 expression in MBMVECs. In addition, acute low-concentration alcohol exposure enhanced migration and proliferation in MBMVECs. The pro-angiogenic effects were significantly attenuated in the presence of TA-02 and LY2109761. On the other hand, two-month low-dose alcohol feeding significantly upregulated TGF β R2 and pTGF β RI in the cerebral cortex. TA-02 and LY2109761 did not alter the vascular density and number of branches in the control mice but significantly reduced the vascular density and number of branches in low-dose alcohol-fed mice under basal conditions. Moreover, low-dose alcohol significantly increased post-ischemic angiogenesis in the peri-infarct cortex. However, the increased angiogenesis was abolished by TA-02 and LY2109761. **Conclusion:** Our findings suggest that TGF β R2 signaling may be critical in LAC-induced cerebral angiogenesis.

Disclosures: P. Subedi: None. U. Subedi: None. H. Sun: None. J. Koticha: None.

Poster

PSTR037: Alcohol: Neurobiological Mechanisms and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR037.16/Z6

Topic: I.08. Learning and Memory

Support: NIH AA020023
NIH AA020024

Title: Adolescent Binge Alcohol Exposure Induces Persistent Transcriptomic and Molecular Changes in Adult Basal Forebrain: A Multi-Modal Approach

Authors: S. VAIDYA¹, R. P. VETRENO², K. KOTLO³, H. KRISHNAN³, M. MAIENSCHNEID-CLINE³, S. C. PANDEY⁴, *F. T. CREWS⁵;

¹Bowles Ctr. for Alcohol Studies, ²Dept. of Psychiatry, Sch. of Med., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; ³Univ. of Illinois at Chicago, Chicago, IL; ⁴Alcohol Res. Center, Dept Psychiatry, Univ. of Illinois at Chicago, Chicago, IL; ⁵UNC Chapel Hill, Chapel Hill, NC

Abstract: Adolescent binge drinking significantly heightens the risk of alcohol use disorder. In the basal forebrain, exposure to adolescent intermittent ethanol (AIE) in rats, which simulates the effects of adolescent binge drinking in humans, triggers pro-inflammatory HMGB1 neuroimmune signalling and decreases the gene expression of cholinergic markers primarily through epigenetic repressive mechanisms. Previous research indicates that anti-inflammatory treatments can restore AIE-induced downregulation of cholinergic gene expression and associated cognitive deficits. To understand the broader transcriptomic changes, we conducted bulk RNA sequencing in the basal forebrain of Wistar rats after AIE (ethanol, 5 g/kg, intragastrically, two days on, two days off, from postnatal days 25 to 55) exposure. We collected forebrain tissues for gene expression analysis when the rats reached adulthood (around PND 90). Gene expression was quantified using featureCounts on Ensembl gene annotations from STAR alignments to the reference genome (rn6). Differential expression statistics were computed using edgeR and Qiagen CLC analysis workbench. Results showed reduced expression of cholinergic markers consistent with previous findings (e.g., *Chat*, *Vacht*, *Ntrk1*) and increased expression of neuroinflammatory genes (*Hmgb211*, *Cxcr4*). Notably, significantly increased *Nr4a1* indicates a potential role in neuroinflammation through the activation of microglia and macrophages. Interestingly, *Vglut1* was upregulated, but no changes were observed in *Vglut2* and other GABAergic genes such as parvalbumin (*Pvalb*) and somatostatin (*Sst*). In a separate cohort following AIE treatment, rats received the HMGB1 inhibitor glycyrrhizic acid (150 mg/L) in drinking water from P56 to P100, with basal forebrain samples collected for molecular assessments. We found that glycyrrhizic acid reversed the loss of cholinergic markers and reversed the AIE-induced upregulation of *Vglut1* expression in qPCR. Further validation of the AIE-induced changes in forebrain gene expression and their connection to cognitive deficits will be presented. Overall, our findings suggest that HMGB1 inhibition can restore the cholinergic phenotype repression by targeting the neuroinflammatory pathway and mitigating the excitatory effects driven by *Vglut1*. For many years, it was believed that the loss of cholinergic neurons due to AIE exposure was irreversible; however, our research indicates that this epigenetically-driven phenomenon may be reversible, which would offer new hope for addressing AIE-induced cholinergic dysfunction.

Disclosures: S. Vaidya: None. R.P. Vetreno: None. K. Kotlo: None. H. Krishnan: None. M. Maienschein-Cline: None. S.C. Pandey: None. F.T. Crews: None.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.01/Z7

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 AA028879
NIH Grant P60 AA006420
NIH Grant R21 AA029498
São Paulo Research Foundation (FAPESP, Grant No. 2022/10168-5;
2018/15505-4)
Pearson Center for Alcoholism and Addiction Research

Title: Effects of short-acting kappa opioid receptor antagonist CYM-53052 on voluntary alcohol intake in intermittent ethanol access female mice

Authors: *M. ALI^{1,5}, P. YOUNG⁵, P. C. BENSING², R. HAN⁵, C. FAVORETTO², M. GUERRERO³, E. ROBERTS⁴, H. ROSEN³, E. P. ZORRILLA²;
²Translational Med., ³Div. of Mol. and Cell. Biol., ⁴Chem., ¹Scripps Res., La Jolla, CA; ⁵Univ. of California San Diego, La Jolla, CA

Abstract: Problematic ethanol drinking has been hypothesized to involve increased activation of central extended amygdala (CeA) and infralimbic dynorphin-kappa opioid receptor (Dyn-KOR) systems, which are implicated in stress, aversion, and negative emotional behavior. Long-acting KOR antagonists, like nor-BNI, accordingly can reduce stress- or withdrawal-associated anxiety and drinking but are not clinically viable. Here, we hypothesized that a translatable, selective, and short-acting KOR antagonist CYM-53052 can reduce binge-like ethanol intake upon renewed access in a model of intermittent, extended voluntary drinking. Adult TRAP2-H2B female mice (n=30) received chronic, intermittent 2-bottle choice access to ethanol (MWF, 24 hr/day, 20%) throughout the 8-week experiment. CYM-53052 was administered during continued access in this paradigm (i.p., 0, 5, 30 mg/kg) in a within-subject design, and intake was measured at 2- and 24-hours post-treatment. CYM-53052 significantly reduced ethanol intake by 2.5 g/kg only at the 30 mg/kg dose (p=0.007) after 2 hours. By 24 hours, drinking was further reduced by 7.1 g/kg (p=0.042). CYM-53052 also significantly decreased preference after 2 hours (p<0.001) (vs. water) at the 30 mg/kg dose. These acute actions of CYM-53052 to reduce ethanol intake and preference were comparable between low- and high- drinkers, as no significant interaction was seen with baseline ethanol intake. The potent, selective short-acting KOR antagonist CYM-53052 acutely reduced ethanol intake and preference in a model of escalated binge-like intake driven by intermittent extended access. The results support further investigation of short-acting KOR antagonists as clinically viable, potential therapeutics for problematic drinking.

Disclosures: M. Ali: None. P. Young: None. P.C. Bensing: None. R. Han: None. C. Favoretto: None. M. Guerrero: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Division of Molecular and Cellular Biology, Scripps Research. E. Roberts: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Division of Molecular and Cellular Biology, Scripps Research. H. Rosen: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Division of Molecular and Cellular Biology, Scripps Research. E.P. Zorrilla: 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 Grants R01 AA028879, P60 AA006420, R21 AA029498, the São Paulo Research Foundation (FAPESP, Grant No. 2022/10168-5; 2018/15505-4), and the Pearson Center for Alcoholism and Addiction Research.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.02/Z8

Topic: H.08. Drugs of Abuse and Addiction

Support: FSU Seed Grant to M.K.

Title: Effects of novel LSD derivatives on alcohol consumption and motivational reward in male and female rats

Authors: *S. K. SALAND^{1,2}, R. HARBIT³, F. DUCLOT^{1,2}, G. BILLAC⁴, C. D. NICHOLS⁵, D. E. NICHOLS⁶, J. SMITH³, M. KABBAJ^{1,2};

¹Biomed. Sci., ²Program in Neurosci., ³Chem. & Biochem., Florida State Univ., Tallahassee, FL; ⁴2A Biosci., New Orleans, LA; ⁵Pharmacol/Exper Therap, LSU Hlth. Sci. Ctr., New Orleans, LA; ⁶Dept Med. Chem & Mol Pharmacol, Univ. of North Carolina at Chapel Hill Eshelman Sch. of Pharm., Chapel Hill, NC

Abstract: Alcohol Use Disorder (AUD) is a chronically relapsing and heterogenous disorder, often marked by persistent anhedonia which is difficult to treat with currently available pharmacotherapies. The need to broaden the spectrum of therapeutic options to target both consumption and co-occurring affective symptoms has spurred a resurgence in interest in psychedelics, such as lysergic acid diethylamide (LSD), for the treatment of AUD and other psychiatric disorders. Though promising, broad utility of LSD as a treatment option is limited by negative side effects, including cardiovascular issues related to activity at the serotonin 5-HT_{2b} receptor. To this end, we have recently synthesized novel LSD derivatives which lack 5-HT_{2b} agonistic activity, including both full (2AB-3006) and partial (2AB-3007) potent 5-HT_{2a} agonists—the latter of which lacks hallucinogenic potential. Here we compared the effects of these compounds on alcohol consumption and chronic alcohol-induced motivational anhedonia in male and female rats. Upon reaching stable levels of baseline drinking using a modified Drinking-in-the-Dark protocol, rats received either 2AB-3006, 2AB-3007, or vehicle in a separate context, and 1h later were allowed 4-h access to 20% ethanol. Motivational reward was subsequently assessed via operant responding under a progressive ratio (PR) schedule of reinforcement. Following task acquisition, daily PR sessions were conducted 5d/week during either drinking or abstinent periods. Following 3d of abstinence, rats received a single injection of either 2AB-3006, 2AB-3007, or vehicle and PR responding was assessed 2h later and for 4d following treatment. Interestingly, 2AB-3006 dose-dependently reduced alcohol consumption acutely in female—but not male—rats, whereas 2AB-3007 was without effect. Likewise, 2AB-

3006, but not 2AB-3007, significantly attenuated chronic alcohol-induced motivational anhedonia for up to 72h post-treatment during abstinence in female rats only. These findings support and warrant further investigation into the therapeutic potential of 2AB-3006 for reducing problematic alcohol consumption and use-related anhedonia, and indicate that hallucinogenic properties may play an important role in some of the therapeutic benefits of psychedelic compounds. Ongoing work seeks to generate comparative efficacy and dose-response profiles of the novel derivatives against LSD and identify brain-wide neuronal activation patterns associated with behavioral efficacy to better understand the mechanisms contributing to these promising outcomes.

Disclosures: **S.K. Saland:** None. **R. harbit:** None. **F. Duclot:** None. **G. Billac:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2A Biosciences. **C.D. Nichols:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2A Biosciences. **D.E. Nichols:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2A Biosciences. **J. Smith:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 2A Biosciences. **M. Kabbaj:** None.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.03/Z9

Topic: H.08. Drugs of Abuse and Addiction

Support: UG3NS128439

Title: Investigating peripheral blood microRNAs as potential biomarkers for cannabinoid receptor occupancy induced by agonist and positive allosteric modulators in mice

Authors: ***S. BHIKULE**¹, D. UPRETI¹, M. MUSTAFA², A. H. LICHTMAN², D. LU¹, R. C. MIRANDA¹;

¹Texas A&M Univ., Bryan, TX; ²Virginia Commonwealth Univ., Richmond, VA

Abstract: Chronic pain, lasting more than three to six months, is a major public health concern affecting millions worldwide and significantly impairing an individual's well-being and quality of life. Although opioids are widely used for pain management, they are associated with serious risks, such as addiction and severe side effects, highlighting the need for safer and more effective alternative therapies. Cannabinoids, natural or synthetic, offer a promising alternative by modulating the endocannabinoid system. They reduce pain perception by binding to cannabinoid type 1 (CB1) receptors in the peripheral and central nervous systems. Small non-coding RNAs, such as circulating miRNAs (circmiRNAs), regulate gene expression and could serve as

biomarkers to predict CB1 receptor occupancy, thereby improving the efficacy of cannabinoid-based therapies for pain management. CirmRNAs are sensitive to molecular changes, signaling, and receptor modulation. Furthermore, cannabinoids influence peripheral blood cell function through both CB1-dependent and CB1-independent pathways. In this study, we aimed to identify peripheral blood miRNAs that serve as biomarkers for CB1 receptor occupancy in mice treated with cannabinoid agonists Tetrahydrocannabinol (THC) and CP-55940, as well as the positive allosteric modulator (PAM) ZCZ011. Plasma samples were collected from wild-type (WT) and CB1 knockout (KO) mice after treatment. miRNA expression was profiled using quantitative RT-PCR and miRNA panels. Differential expression analysis was conducted using independent t-tests, with significant miRNAs identified based on a p-value < 0.2, Cohen's d > 0.4, and a 95% confidence interval (CI). Preliminary findings indicate that 6 miRNAs were differentially expressed in WT mice treated with THC, 12 in WT mice treated with CP-55940, and 8 in WT mice treated with ZCZ011, all of which were CB1-dependent. Additionally, 4 miRNAs were differentially expressed in CB1 KO mice treated with THC, and another 4 in CB1 KO mice treated with ZCZ011. These findings suggest that most miRNA changes in WT mice were CB1-dependent, suggesting that CB1 receptor occupancy plays a major role in modulating these effects. However, some miRNA changes in CB1 KO mice indicate the involvement of CB1-independent pathways. These findings highlight the potential of specific miRNAs as biomarkers for CB1 receptor occupancy and cannabinoid activity, further emphasizing the importance of CB1-dependent mechanisms in pain modulation. Further studies will explore the role of these miRNAs in biological pathways associated with pain management.

Disclosures: S. Bhikule: None. D. Upreti: None. M. Mustafa: None. A.H. Lichtman: None. D. Lu: None. R.C. Miranda: None.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.04/Z10

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA DA000069

Title: Differential Abuse Liability and Therapeutic Potential of Ketamine Enantiomers

Authors: *M. R. LEVINSTEIN¹, R. BUDINICH¹, S. EWBANK⁴, I. SCHOENBORN¹, O. SOLÍS CASTREJÓN², T. DI IANNI⁶, J. BONAVENTURA⁷, C. A. ZARATE, Jr.⁸, Y. SHAHAM³, R. AIRAN⁵, M. MICHAELIDES¹;

¹NIH, NIDA IRP, Baltimore, MD; ²NIH, NIDA IRP, BALTIMORE, MD; ³Behavioral Neurosci. Br., NIH, NIDA IRP, Baltimore, MD; ⁵Radiology, ⁴Stanford Univ., Stanford, CA; ⁶Univ. of California San Francisco, San Francisco, CA; ⁷Univ. de Barcelona, Barcelona, Spain; ⁸Div. Intramural Res. Program, NIMH, Bethesda, MD

Abstract: (R,S)-ketamine has been used as an analgesic, anesthetic, and antidepressant. (S)-ketamine is FDA-approved for treatment-resistant depression, while (R)-ketamine shows promising antidepressant efficacy with fewer psychotomimetic effects. Both enantiomers are regarded as noncompetitive NMDAR antagonists, but they also interact with other receptors. (S)-ketamine has about fourfold higher affinities at NMDARs and μ opioid receptors (MORs) than (R)-ketamine. Recently, our lab found that while rats will learn to self-administer (S)-ketamine at 0.5 mg/kg/inf dose, they will not learn to self-administer (R)-ketamine at this dose. We also showed that this dose of (S)-ketamine increased brain activity in the nucleus accumbens (NAc). Repeated (S)-ketamine affects MOR density and function. We investigated (R)-ketamine's effects using equimolar and equipotent doses to (S)-ketamine. We also have shown that MOR activation drives (S)-ketamine's abuse liability and repeated administration of (S)-ketamine decreases subsequent heroin reinforcement. We now investigate (S)-ketamine's ability to curb heroin seeking in dependent rats. Rats acquired (R)-ketamine IVSA at 2 mg/kg/infusion (4x higher than S-ketamine) with peak responding at 1 mg/kg/inf. Naltrexone significantly blunted this response at 1 and 0.5 mg/kg doses. MK-801 decreased (R)-ketamine infusions at 1 mg/kg dose. Functional ultrasound imaging was used to measure brain-wide changes in cerebral blood volume. Rats were pretreated with saline or naltrexone followed by a single IV injection of saline or (R)-ketamine 15 min later while imaging the mPFC and NAc. Unlike (S)-ketamine, (R)-ketamine (0.5 or 2 mg/kg) caused no NAc activity changes. However, 2 mg/kg (R)-ketamine increased activity in cingulate cortex and secondary motor cortex. Another group of rats were catheterized and underwent IVSA of heroin. They were then tested for heroin seeking and then divided into groups to receive 8 days of saline or (S)-ketamine. Rats receiving 8 days of (S)-ketamine showed significantly decreased heroin seeking compared to saline controls at 24 hours post-treatment. In another cohort of rats, we implanted optic fibers coated in a mixture of the dopamine sensor, AAV9-hsyn-GRAB_{DA}, into the nucleus accumbens. We plan to inject the rats with (S)- or (R)-ketamine and record dopamine transients. Our findings indicate that (R)-ketamine has reinforcing effects at sufficiently high doses and these effects may be due to its effects on the opioid system with different regional brain activity patterns than (S)-ketamine. (S)-ketamine decreases heroin seeking, suggesting potential for treating opioid use disorder.

Disclosures: **M.R. Levinstein:** None. **R. Budinich:** None. **S. Ewbank:** None. **I. Schoenborn:** None. **O. Solís Castrejón:** None. **T. Di Ianni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Attune Neurosciences, Inc. F. Consulting Fees (e.g., advisory boards); Attune Neurosciences, Inc. **J. Bonaventura:** None. **C.A. Zarate:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent for the use of (2R,6R)-hydroxynorketamine, (S)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of ketamine in the treatment of depression and neuropathic pain, Patent application for the use of (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and PTSD. **Y. Shaham:** None. **R. Airan:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; AbbVie, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cordance Medical, Lumos Labs. F. Consulting Fees (e.g., advisory boards); Cordance Medical, Lumos Labs. **M. Michaelides:** 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.; AstraZeneca, Redpin Therapeutics, Attune Neurosciences, Inc.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.05/Z11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 DA061773
NIH/NIDA R00 DA048970
NIH/NIDA UH3 DA050316
DOD W81XWH-22-1-0266-PR211151
University of Minnesota Foundation AP-0323-04
NIH/NIDA P30DA048742
NIH/NIDA F31 DA062411

Title: The Kinase GRK2/3 Mediates β -arrestin Recruitment to the Neurotensin Receptor 1 by Biased Intracellular Ligands

Authors: *M. N. MOORE¹, L. M. SLOSKY², V. ROBLETO³, C. KRUSEMARK⁴, S. OLSON⁵, S. DUTTA⁶;

¹Pharmacol., Univ. of Minnesota, Saint Paul, MN; ²Pharmacol., Univ. of Minnesota, Minneapolis, MN; ³Univ. of Minnesota, Saint Paul, MN; ⁴Pharmacol., Univ. of Minnesota, Fairmont, MN; ⁵Ctr. for Chem. Genomics, ⁶Sanford Burnham Med. Discovery Inst., La Jolla, CA

Abstract: The neurotensin receptor 1 (NTSR1) is a G protein-coupled receptor (GPCR) and promising therapeutic target. Balanced NTSR1 stimulation results in Gq activation, leading to calcium mobilization, and β -arrestin recruitment, leading to receptor trafficking. The β -arrestin biased allosteric modulator SBI-553 agonizes β -arrestin but not Gq. SBI-553 attenuates addiction-associated behaviors in animals without the side effects of balanced agonists, suggesting that compounds in this class can serve as the basis for more selective therapeutics. The mechanism by which SBI-553 stimulates receptor- β -arrestin association, however, is not well understood. Canonically, ligand-induced recruitment of β -arrestin is preceded by the recruitment of GPCR kinases, including the kinase GRK2, which phosphorylate residues on the receptor's C-terminal tail. Recruitment of GRK2 is preceded, in turn, by G protein activation and the binding of dissociated G $\beta\gamma$ to GRK2. Here, we demonstrate that SBI-553-stimulated β -arrestin recruitment requires GRK2 and that stabilization of the NTSR1-SBI-553-GRK2 complex leads to improved β -arrestin activity. In HEK293T cells, both NT and SBI-553 stimulated phosphorylation of the same 7 residues on NTSR1's C-terminus. Iteratively mutating these residues to non-phosphorylatable alanines impaired NT- and SBI-553-induced β -arrestin

recruitment. Both NT- and SBI-553-induced β -arrestin recruitment was impaired in HEK293 cells lacking GRK2/3 but not GRK5/6. SBI-553-induced β -arrestin recruitment was enhanced by GRK2 overexpression, which produced a 10-fold leftward shift in SBI-553's concentration response curve. To explore the consequences of this potency shift, we monitored NTSR1 internalization. GRK2 overexpression enhanced SBI-553-induced internalization in genetically intact cells and rescued an internalization impairment in the combination GRK2/3/5/6-null line. A recently published structure of the complex shows SBI-553 binding within NTSR1's core and direct intermolecular contacts with GRK2. Preliminary structure-activity-relationship studies with SBI-553 analogs suggest that a molecule's GRK2 and β -arrestin recruitment potencies are correlated and can be enhanced by targeted changes to the SBI-553 scaffold using structure-based design strategies. Together, these data suggest that GRK2/3 are key regulators of SBI-553 compound series potency and provide a novel means of generating compounds with diverse β -arrestin activity profiles.

Disclosures: M.N. Moore: None. L.M. Slosky: None. V. Robleto: None. C. Krusemark: None. S. Olson: None. S. Dutta: None.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.06/Z12

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 DA061773
NIH/NIDA R00 DA048970
NIH/NIDA UH3 DA050316
DOD W81XWH-22-1-0266-PR211151
University of Minnesota Foundation AP-0323-04
NIH/NIDA P30DA048742

Title: Intracellular GPCR ligands change G protein subtype selectivity by restricting transducer access to the receptor core

Authors: *K. L. PERSON¹, M. N. MOORE¹, V. ROBLETO¹, A. ALWIN¹, C. KRUSEMARK¹, N. FOSTER¹, C. RAY², A. INOUE³, M. R. JACKSON⁴, L. S. BARAK², E. MARRON¹, S. H. OLSON⁴, L. M. SLOSKY¹;

¹Pharmacol., Univ. of Minnesota, Minneapolis, MN; ²Cell Biol., Duke Univ., Durham, NC;

³Grad. Sch. of Pharmaceut. Sci., Tohoku Univ., Sendai, Japan; ⁴Conrad Prebys Ctr. for Chem. Genomics, Sanford Burnham Prebys Med. Res. Inst., La Jolla, CA

Abstract: G protein-coupled receptors (GPCRs) modulate neuronal activity through the activation of one or more $G\alpha$ proteins. The discovery of compounds that bias receptor signaling away from one $G\alpha$ protein subtype and toward another will permit the separation of on-target

therapeutic benefits and undesired side effects. The rational design of such compounds, however, has proven difficult. We hypothesized that small molecules binding the GPCR-transducer interface could change G protein subtype selectivity by direct intermolecular interactions rather than long-distance conformational changes. To test this, we examined the class A GPCR neurotensin receptor 1 (NTSR1), a receptor for which an intracellular small molecule allosteric modulator has been identified: SBI-553. While Gq-preferring, NTSR1 is promiscuous, activating at least 12 different G proteins. SBI-553 antagonizes neurotensin (NT)-induced activation of some G proteins (e.g., Gq) but does not antagonize and weakly agonizes others (e.g., Go, G12/13), biasing NTSR1 toward both β -arrestin recruitment and alternative G protein coupling. Here, we define the molecular mechanism by which SBI-553's bias is achieved and use this mechanism to design compounds with distinct G protein selectivity profiles. Cell-based assays of NTSR1-Gq association demonstrate that SBI-553 fully antagonizes NT-NTSR1 Gq activation by preventing NTSR1-Gq coupling. Critically, in β -arrestin1/2-null cells, SBI-553's Gq antagonism remains intact, suggesting that it may result from direct occlusion of Gq's binding determinants. In line with this conclusion, exchanging the 5 C-terminal, NTSR1-interacting amino acids of Go for those of Gq is sufficient to reverse sensitivity to SBI-553 antagonism. Recently published cryo-EM structures of NT:NTSR1:mini-Go demonstrate that, in the presence of SBI-553, the Go C-terminus adopts an alternative, shallow-binding 'open' conformation to accommodate the small molecule. Homology models suggest that this shallow-binding conformation is more energetically favorable for some G protein subtypes (e.g., Go, G12/13) than others (e.g., Gq), with stability measures correlating with extent of antagonism and agonism. SBI-553 appears to act as both a molecular bumper and a glue, sterically excluding some transducers while promoting association with others. Leveraging structural models, we designed new compounds with distinct G protein subtype selectivity profiles and in vivo activities. These data suggest that signaling bias can be rationally designed using small molecules that change transducer access to the receptor core, a novel approach applicable to the diverse GPCR superfamily.

Disclosures: K.L. Person: None. M.N. Moore: None. V. Robleto: None. A. Alwin: None. C. Krusemark: None. N. Foster: None. C. Ray: None. A. Inoue: None. M.R. Jackson: None. L.S. Barak: None. E. Marron: None. S.H. Olson: None. L.M. Slosky: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanford Burnham Prebys Medical Research Institute (SBP) and Duke University.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.07/AA1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 DA061773
NIH/NIDA R00 DA048970
NIH/NIDA UH3 DA050316

DOD W81XWH-22-1-0266-PR211151
University of Minnesota Foundation AP-0323-04
NIH/NIDA P30DA048742

Title: Missed by G protein heterotrimer dissociation assays, Neurotensin Receptor 1 activates GαS to elevate cellular cAMP levels

Authors: *V. L. ROBLETO¹, K. L. PERSON¹, M. N. MOORE¹, S. OLSON², L. M. SLOSKY¹;

¹Dept. of Pharmacol., Univ. of Minnesota, Minneapolis, MN; ²Conrad Prebys Ctr. for Chem. Genomics, Sanford Burnham Prebys, San Diego, CA

Abstract: The neurotensin receptor 1 (NTSR1) controls nervous system functions, including the regulation of blood pressure, body temperature, pain, and reward. As a G protein-coupled receptor (GPCR), NTSR1 signals through the activation of heterotrimeric G proteins, with agonist binding canonically stimulating the dissociation of the Gα from the Gβγ subunits. There are 16 non-visual Gα proteins that fall into four families (i.e., Gαq, Gαs, Gαi, Gα12/13). These families differentially engage second messenger systems, leading to distinct cellular and physiological effects. While NTSR1 preferentially couples to the Gαq, it is promiscuous, activating most Gα subtypes across families. The extent to which NTSR1 activates Gαs, however, remains poorly understood. In recent studies in HEK293T cells using TRUPATH and Gβγ/GRK3 association assays, which detect G protein activation via heterotrimer dissociation, NTSR1 activated every Gα subtype profiled, except for Gαs. Indeed, we observe that NTSR1 does not activate TRUPATH GαS sensors, neither with the reported optimal Gβγ pairing nor with the 12 possible combinations of Gαs-β-γ pairings. In contrast, we detect robust Gαs engagement and signaling using alternative, non-G protein dissociation-based methods. Following neurotensin (NT) application, NTSR1 activated the Gαs sensor in a TGFα shedding-based assay, promoted mini Gαs recruitment to NTSR1, and elevated cAMP levels in HEK293T cells, as detected by an EPAC biosensor. To explore why NTSR1-Gαs activation is missed in dissociation-based assays, we first validated Gαs TRUPATH sensor function using the Gs-preferring β2AR and D1 receptors. We confirmed that NTSR1-mediated cAMP production was mediated by Gαs. NTSR1-mediated elevations in cAMP levels were lost in G protein-deficient cells and rescued by Gαs but not Gαq re-expression. While NT-induced dissociation of the Gs heterotrimer was not detected by the TRUPATH sensors, these sensors did rescue NT-induced cAMP elevation in G protein-deficient cells, suggesting activation and function. Together with reports that NTSR1 stimulates Ca²⁺-independent cAMP accumulation in CHO cells and adenylylate cyclase inhibitors attenuate effects of NT on neuronal activity, our data support the conclusion that NTSR1 activates Gαs. This activation is not detected by widely used platforms that rely on subunit dissociation, suggesting the possibility of signaling by an intact Gs heterotrimer: a rare but not unprecedented phenomenon. As a lack of Gs activation has been reported for many Gq-preferring class A GPCRs based on heterotrimer dissociation assays, a revisiting of GPCR-Gs activation using orthogonal assays is warranted.

Disclosures: V.L. Robleto: None. K.L. Person: None. M.N. Moore: None. S. Olson: None. L.M. Slosky: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanford Burnham Prebys Medical Research Institute (SBP) and Duke University.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.08/AA2

Topic: H.08. Drugs of Abuse and Addiction

Support: UG3NS115637
1UG3NS114438

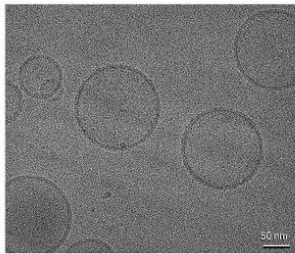
Title: Focused Ultrasound-Triggered Clonidine Delivery Enables Region-Specific Neuromodulation with Potential for Treating Neuropsychiatric Disorders

Authors: P. MA¹, P. MARTINEZ¹, *Y. XIANG³, K. SINHA ROY¹, M. PUROHIT¹, R. AIRAN²;

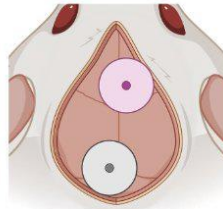
²Radiology, ¹Stanford Univ., Stanford, CA; ³Stanford Med. Dept. of Radiology, Stanford, CA

Abstract: Adrenergic modulation with drugs like clonidine has shown promise for treating varied neuropsychiatric diseases, yet side effects due to off-target action in the brain and body limit its utility, supporting the need for noninvasive, region-specific clonidine delivery. We developed focused ultrasound (FUS)-sensitive liposomes that release clonidine at targeted brain sites, enabling millimeter-precision pharmacologic neuromodulation noninvasively with limited systemic drug exposure. Liposomes were formulated from HSPC:DSPE-PEG2000:cholesterol (52.8:42.3:4.8) and loaded with clonidine using a transmembrane ammonium sulfate gradient. Internal sucrose content was varied to optimize stability and acoustic response. Long-term stability, in vitro release, and in vivo effects were evaluated. The liposomes (~175 nm, PDI<0.1) showed minimal free drug and uniform spherical morphology under TEM (A). FUS significantly enhanced clonidine release versus passive diffusion, with retained responsiveness >120 days (C Left). In vivo clonidine uncaging at the medial prefrontal cortex (mPFC) led to dose-dependent drug accumulation at the desired site (B), with minimal off-target exposure and improved target-background delivery with sucrose incorporation (C middle). Free clonidine showed no spatial selectivity while clonidine delivery was restricted to the sonicated site with the FUS-sensitive liposomes (C right), confirming the localized drug uncaging performance enabling targeted pharmacodistribution. Free clonidine and brainstem uncaging caused marked hypotension with no blood pressure change with mPFC uncaging (D) confirming that this approach yields selective functional activation of neuropsychiatrically active drugs like clonidine. Our findings support that this nanotechnology enables noninvasive, targeted pharmaco-neuromodulation while minimizing toxicity, opening avenues for more targeted use of clonidine and similar neuromodulators for neuropsychiatric disorders.

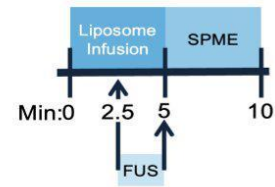
A TEM imaging



B In vivo FUS design

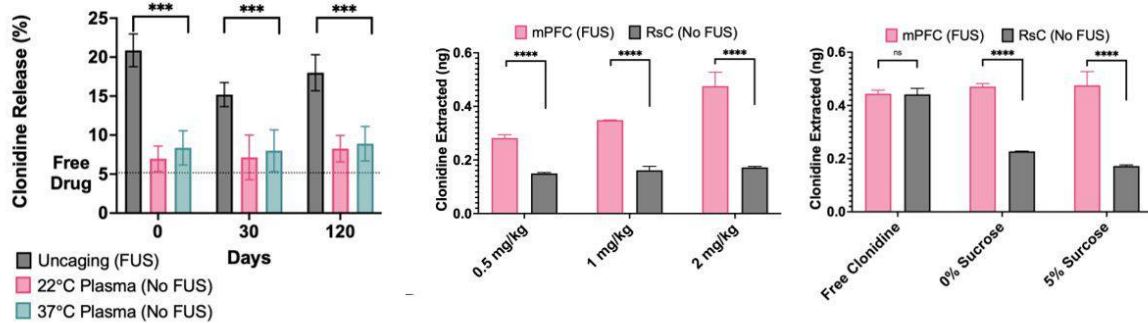


FUS @ mPFC vs Stem

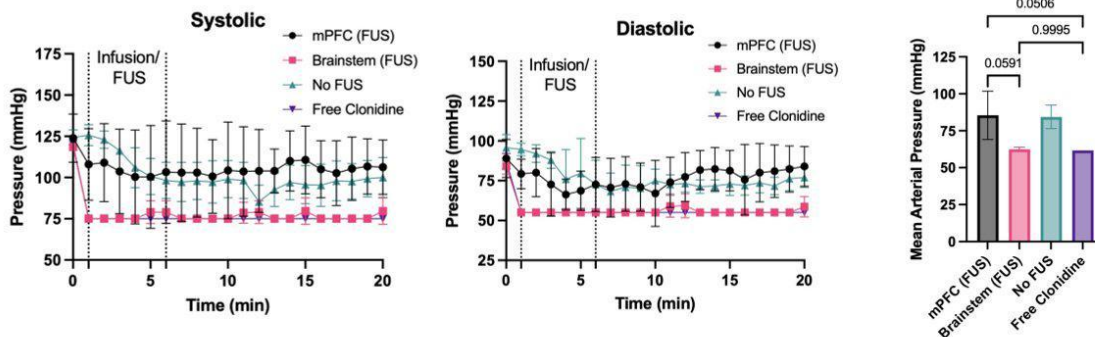


FUS & SPME timeline

C In vivo and in vitro clonidine release



D Blood pressure response to regional delivery



Disclosures: P. Ma: None. P. Martinez: None. Y. Xiang: None. K. Sinha Roy: None. M. Purohit: None. R. Airan: None.

Poster

PSTR038: Developing Treatments for Alcohol and Drug Addiction

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR038.09/AA3

Topic: H.08. Drugs of Abuse and Addiction

Title: Involvement of the histaminergic system on maladaptive feeding behavior in an animal model of binge eating in female rats

Authors: M. V. MICIONI DI BONAVENTURA¹, E. MICIONI DI BONAVENTURA¹, L. BOTTICELLI¹, G. EINAUDI¹, Z. KOZIARA¹, A. COSTA³, G. PROVENS⁴, *C. CIFANI²;
¹Sch. of Pharmacy, Pharmacol. Unit, ²Sch. of Pharm., Univ. of Camerino, Camerino, Italy;
³Univ. of Florence, Firenze, Italy; ⁴Dept. di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Univ. degli Studi di Firenze, Firenze, Italy

Abstract: Binge eating disorder (BED) is the most common eating disorder, marked by recurrent episodes of excessive food intake within a short time frame, accompanied by a perceived loss of control over eating behavior. To date, lisdexamfetamine dimesylate remains the only FDA-approved pharmacotherapy for BED, highlighting the urgent need for novel therapeutic approaches. Emerging evidence points to a role for neuronal histamine in regulating stress responses and feeding behavior. In this study, we examined alterations in the histaminergic (HA) system at the gene expression level and evaluated the effects of a histamine-targeting compound in a well-characterized preclinical model of binge eating. Binge-like eating behavior was induced in female Sprague-Dawley rats through intermittent cycles of food restriction/refeeding combined with a frustration stress procedure and exposure to highly palatable food. Following repeated binge episodes, animals were sacrificed, and specific brain regions were collected for RT-PCR analysis of HA-related gene expression. Additionally, both acute and chronic treatments aimed at enhancing HA neurotransmission were tested in the same animal model. We observed significant changes in mRNA expression of HA receptors and histamine-metabolizing enzymes in various brain regions of binge eating rats compared to controls. Notably, pharmacological enhancement of HA transmission, both acutely and chronically, effectively suppressed binge-like behavior and prevented several of the associated molecular alterations. These findings suggest a potential involvement of the HA system in the pathophysiology of binge eating and support its consideration as a novel pharmacological target for BED treatment.

Disclosures: M.V. Micioni Di Bonaventura: None. E. Micioni Di Bonaventura: None. L. Botticelli: None. G. Einaudi: None. Z. Koziara: None. A. Costa: None. G. Provensi: None. C. Cifani: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.01/AA4

Topic: I.03. Decision Making

Support: NSF Career Grant #2235858
NIH/NIDA Grant #R01DA058653
NDSEG Fellowship

Title: Computational Primitives for Cost-Benefit Decision-Making

Authors: *L. RAKOCEVIC¹, A. FRIEDMAN²;

¹Univ. of Texas at El Paso, El Paso, TX; ²Biological Science, UTEP, El Paso, TX

Abstract: Cost-benefit decision-making is a critical process performed by all organisms, including humans. Various factors, including risk, uncertainty, age, sex, and neuropsychiatric disorders can alter decision-making. Though decision-making is used as a trans-diagnostic symptom for multiple disorders, including substance-use disorder, post-traumatic stress disorder, depression, Alzheimer's, Parkinson's, and Huntington's Disease, it differs wildly across and even within individuals. This variability makes it difficult to quantify decision-making objectively and computationally, impeding diagnosis and treatment. To examine the heterogeneity of cost-benefit decision-making in humans, we developed a comprehensive task and analysis framework that presents participants with a series of approach-avoid trade-offs across a variety of contexts. Our task battery included: 1) an approach-avoid task which weighs situational costs and benefits, 2) a social task which weighs interpersonal costs and benefits, 3) a moral task which weighs ethical rights and wrongs, and 4) a probabilistic task which uses the same costs and benefits as in approach-avoid but introduces an element of chance when achieving the outcome. Data was also collected from rodents performing a similar approach-avoid decision-making task. We found that across 35 human participants and 42 rodents doing four approach-avoid decision-making tasks, nearly all decision-making behaviors observed fit within a set of discrete and heterogeneous decision-making strategies. These strategies, used to weigh costs and rewards, were termed 'decision-making primitives'. We find that utilization of these primitives in both rodents and humans shifts based on factors like hunger, tiredness, and sex, and that individuals use primitives differently. Furthermore, these distinct primitives can be differentiated using physiological features like eye movement and heart rate. We additionally demonstrate that using a naturally-inspired neural network architecture generates output that overlaps with human and rodent performance while a non-constrained neural network does not. This novel conceptual framework, by isolating discrete 'decision-making primitives', has the potential to help us identify how different brain regions give rise to decision-making behavior, as well as to facilitate better diagnosis and treatment of neuropsychiatric disorders through the quantification of decision-making. This project was supported by the NSF/CAREER (#2235858), NIH/NIDA (#R01DA058653), and the NDSEG fellowship to Lara Rakocevic.

Disclosures: L. Rakocevic: None. A. Friedman: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.02/AA5

Topic: I.03. Decision Making

Support: Ministry of Education, Government of India
Pratiksha Trust

Title: Task-dependence of network-to-network variability in learning, performance, and dynamics of heterogeneous recurrent networks

Authors: *A. SANTHOSH¹, R. NARAYANAN^{2,1};

¹Brain, Computation, and Data Sci., ²Mol. Biophysics Unit, Indian Inst. of Sci., Bengaluru, India

Abstract: Artificial recurrent networks (ARNs) are endowed with the ability to efficaciously process time-dependent information through feedback connections. Although ARNs have been useful in studying neural dynamics and representation of complex cognitive tasks, their composition and training protocols lack several features of brain networks. Chief among the several lacunae in ARN units is the absence of pronounced heterogeneities that biological neurons manifest. Here, we implemented a systematic framework to analyze task-dependence of the impact of neural heterogeneities on recurrent networks. We initialized multiple ARNs (200 units) with six levels of intrinsic heterogeneity in time constants (H0-H5), with H0 representing homogeneous networks and H5 being the highest heterogeneity level. We trained these ARNs using a reward-modulated Hebbian learning algorithm to perform six different cognitive tasks - Go, DlyGo, Anti, DlyAnti, MSDM, and DlyMSDM - one at a time. We compared the number of training trials required for convergence, task performance, and task-execution dynamics of the trained networks across levels of heterogeneities and hyperparameters. We found network-to-network variability in the impact of intrinsic heterogeneity on each metric. Importantly, network-to-network variability was pronounced in networks trained on complex tasks (memory tasks such as DlyGo), compared to those trained on simpler tasks (memoryless tasks such as Go). Finally, we tested these trained networks by introducing several post-training heterogeneities (in a graded fashion from P0 to P5) by altering the time constants, recurrent synaptic weights, initial activity, trial duration, activity perturbation, and the task performed. Of all the post-training heterogeneities tested, we found synaptic jitter to be the most detrimental. We found the robustness of these networks to depend critically on network initialization, intrinsic heterogeneity level, and task complexity. Overall, our analyses caution against strong generalizations on the impact of heterogeneities on training, performance, and resilience of ARNs, given the strong dependence of such impact on several factors including level of heterogeneities, form and extent of perturbations, network hyperparameters, and the specific task being executed. These observations strongly advocate a complex system framework to study the impact of neural heterogeneities on circuit function. In particular, we emphasise the need to focus on the global structure and interactions among different forms of heterogeneities in a system, rather than focusing on any one form of neural-circuit heterogeneity.

Disclosures: A. Santhosh: None. R. Narayanan: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.03/AA6

Topic: I.03. Decision Making

Support: NIMH R01MH128187

Title: Comparing Reinforcement Learning Models to Explain Human Neural and Behavioral Measures of Decision-making Under Risk

Authors: *N. SHAHDOUST¹, R. COWAN², A. PRICE³, T. DAVIS³, B. SHOFTY², J. D. ROLSTON⁴, S. RAHIMPOUR², E. H. SMITH²;

¹Electrical and Computer Engin., ²Neurosurg., ³Univ. of Utah, Salt Lake City, UT; ⁴Neurosurg., Brigham and Women's Hosp., Newton, MA

Abstract: Understanding how the human brain encodes and computes value during decision-making under risk is essential for interpreting behavior outcomes and their neural correlates. To investigate this, we introduce the Starling Task, a novel paradigm in which participants are presented with the back of two cards, each belonging to a known deck type where the color signals the statistical distribution of that deck. Each deck contains cards numbered from 1 to 9, however the frequency of each card varies. Orange (Low) deck is skewed towards low numbers (i.e. 1, 2). In the Green (High) deck is skewed towards high numbers. Both the participant and virtual opponent draw a card from the same deck type (card values never match). Participants then decide whether their own card is likely higher or lower than the opponent's based on the visible card and known deck distributions. Correct responses earn +0.5; incorrect ones incur -0.5. The task includes 45 trials for each uniform, low/high, and high/low deck types (with low/high order randomized per subject), followed by 135 trials randomized across all three decks, totaling 270 trials. Patients undergoing invasive monitoring for medically refractory epilepsy at the University of Utah Hospital performed the task in their hospital rooms while recording from intracranially from temporarily implanted electrodes. Healthy participants performed the online version of the task through our lab website (www.neurosmiths.org). We analyzed behavior in both healthy and epileptic participants as well as neural activity in the epileptic patients' brain recorded via depth electrodes implanted in decision-related brain areas including the anterior cingulate cortex (ACC), and hippocampus.

We fit multiple reinforcement learning models to behavioral and neural data: Win-Stay-Lose-Shift, Rescorla-Wagner with Greedy and SoftMax policies, and two risk-sensitive models; one with a single value function and a Dual-Q model that separates reward and risk with distinct learning rates (α_r , α_s) and a risk sensitivity parameter (η). Model comparisons show that risk-sensitive models more accurately explain both behavioral variability and trial-by-trial neural dynamics (Models McFadden- $R^2 \pm$ S.E.M; WSLs: 0.007 ± 0.002 , Greedy: 0.23 ± 0.01 , SoftMax: 0.31 ± 0.01 , Dual-Q: 0.35 ± 0.01 , RS: 0.40 ± 0.01). We also correlate individual model parameters with neural responses to uncover mechanistic links between decision behavior and

electrophysiological activity. The results utilize computational characterization of decision-making behavior across trials to show how human decision-making under risk with known distributions is represented in the brain.

Disclosures: N. Shahdoust: None. R. Cowan: None. A. Price: None. T. Davis: None. B. Shofty: None. J.D. Rolston: None. S. Rahimpour: None. E.H. Smith: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.04/AA7

Topic: I.03. Decision Making

Support: MIC grant JPMI00316
JSPS KAKENHI JP24K15188
JSPS KAKENHI JP25H01365

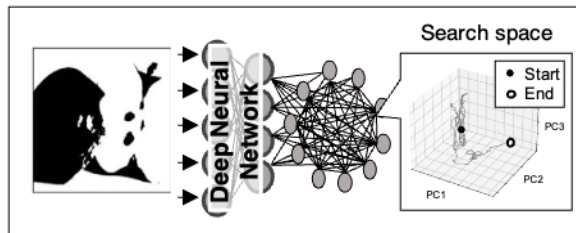
Title: Simulating time until eureka moment using a recurrent neural network

Authors: *M. KIMURA^{1,2}, Y. MATSUSHITA³, S. SENO⁴, T. MURATA², I. OHZAWA⁴, T. YANAGIDA², K. KANEKO⁵, K. HOSODA²;

¹Univ. of Hyogo, Akogun. Hyogo, Japan; ²Natl. Inst. of Information and Communications Technol., Osaka, Japan; ³Natl. Ctr. for Biological Sci., Bangalore, India; ⁴Osaka Univ., Osaka, Japan; ⁵Niels Bohr Inst., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Insight is typically understood as a reorganization of known elements to generate novel solutions to previously unlearned problems. While neuroscientific studies have made progress in identifying the brain regions involved in insight, the manner in which these regions collectively construct the neural system underlying insight remains poorly understood. Moreover, existing computational models often either oversimplify experimental phenomena or rely on complex architectures that are detached from empirical data. To date, no neural network-based model has matched the input-output structure of human experimental tasks used in behavioral studies. In this study, we propose a biologically inspired model that simulates the temporal dynamics underlying visual insight, particularly in the recognition of highly degraded stimuli known as Mooney images. The model comprises two main components: a deep neural network (DNN) module for the extraction of visual features, and a recurrent neural network (RNN) that engages in a chaotic search process (see Figure). This RNN is governed by time-dependent differential equations and proceeds autonomously, terminating when the internal reconstruction of the degraded visual features is achieved. As a result, the proposed model successfully reproduces the statistical properties of human reaction times (RTs) when tested on the same image set employed in psychophysical experiments. Specifically, it captures (i) the lognormal-like distribution of RTs across participants, (ii) the proportional relationship between log-scaled RT mean and standard deviation across images, and (iii) the discrete structure in

image difficulty. Notably, the slope of this proportional relationship closely matched empirical data, a pattern that could not be explained by previous coarse-grained models. These findings may suggest a potential link between chaotic neural dynamics and the cognitive mechanisms that underlie human insight, and they provide a computational framework toward implementing insight-like functionality in artificial systems.



Disclosures: M. Kimura: None. Y. Matsushita: None. S. Seno: None. T. Murata: None. I. Ohzawa: None. T. Yanagida: None. K. Kaneko: None. K. Hosoda: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.05/AA8

Topic: I.03. Decision Making

Support: NIMH - ZIAMH002988
NSF-2141860

Title: Attending and introspecting: a computational measure of metacognitive ability relates to attentional control

Authors: *S. M. TROWBRIDGE¹, O. VEGAS², S. LOPEZ-GUZMAN⁴, M. GRUBB³;
¹Unit on Computat. Decision Neurosci., Natl. Inst. of Mental Hlth., Bethesda, MD; ³Psychology, Trinity Col., Hartford, CT; ⁴Unit on Computat. Decision Neurosci., Natl. Inst. of Mental Hlth. Div. of Intramural Res., Bethesda, MD

Abstract: Attentional Blink (AB) is the decreased ability to detect a second target when it follows an initial target by ~200ms. Interestingly, meditation appears to diminish the effect of AB. We wanted to test whether having to introspect about one's choices, a process known as metacognition, would similarly ameliorate the AB. Further, we hypothesized that individual differences in metacognitive ability could limit the effect of metacognition on AB. Here, we addressed these questions by measuring AB before and after completing a task where subjects engaged in metacognition. 186 participants, split across three groups (confidence task /control task/no task), completed the experiment online through Prolific. AB was measured using a rapid serial visual presentation task, where participants viewed a fast stream of visual stimuli and had to identify an initial target (T1) before reporting on the presence of a second target (T2).

Participants completed the AB before and after the perceptual decision-making task. In the perceptual decision-making task, participants were presented with four Gabors, three oriented vertically at 0° and one tilted to the left or right by a range of 0.5°-30°. Participants in all three groups indicated whether the tilted Gabor was rotated to the left or right. The confidence task group then reported their confidence that they were correct on a 1-4 scale, the control task group reported on the location of the tilted Gabor, and the no task group made no secondary report. AB data was fit to a signal detection theory (SDT) based linear model through hierarchical Bayesian estimation, to derive individual-level decision criterion and decision sensitivity parameters and their change after performing the perceptual task. Confidence data from the perceptual task was fit to a computational process model of confidence (CASANDRE) to derive individual parameters of metacognitive ability. At the group level, SDT modeling revealed a shift towards a more conservative AB decision criterion in the confidence task group, but not the other two groups, suggesting when individuals engage in introspection, they become more cautious in other tasks. Both the confidence group and the no task group showed an increase in decision sensitivity, indicating an improvement in performance was likely due to repetition rather than the metacognitive intervention. At the individual level, those with greater metacognitive ability displayed higher baseline decision sensitivity in the AB. Given that greater metacognitive ability is related to enhanced attentional control, future studies could address whether metacognition and visual attentional control share common mechanisms.

Disclosures: S.M. Trowbridge: None. O. Vegas: None. S. Lopez-Guzman: None. M. Grubb: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.06/AA9

Topic: I.03. Decision Making

Support: NIH Annual Report Number ZIAMH002981

Title: Relating emotional monitoring and control to metacognition and choice behavior in risky decision-making

Authors: *J. H. TRUDEAU¹, C.-H. KAO¹, C. E. HAEFFNER², S. TROWBRIDGE³, S. LOPEZ-GUZMAN⁴;

¹Natl. Inst. of Mental Health, NIH, Bethesda, MD; ²NIH, Bethesda, MD; ³Natl. Inst. of Mental Hlth., Bethesda, MD; ⁴Unit on Computat. Decision Neurosci., Natl. Inst. of Mental Hlth. Div. of Intramural Res., Bethesda, MD

Abstract: Background Emotional experience can guide behavior. The ability to track emotional experience includes both monitoring subjective feelings and repairing emotional state, described as emotional awareness and control. The ability to track one's decision quality is known as

metacognition. Recent advances derive computational measures of metacognitive ability for subjective decisions involving risk (Plate et al., bioRxiv, 2025). However, the extent to which metacognitive monitoring in decision-making relates to emotional abilities is not yet understood. Here, we evaluate how metacognition and choice behavior in risky decision making relate to emotional awareness and control. **Methods** 73 adults completed a risky decision-making task. Participants chose between a certain monetary gain or loss of \$5 versus a lottery to win or lose a different amount (or nothing). The lottery amounts, probabilities, and ambiguity levels varied trial-by-trial. After making their choice, participants rated their confidence that they chose what they preferred. We sequentially fit a utility model to the task choices and a computational process model of confidence (CASANDRE) to extract individual parameters for metacognitive ability. Participants completed the Interoceptive Accuracy Questionnaire, Trait Meta-Mood Scale, Toronto Alexithymia Scale, Mindful Attention Awareness Scale, General Self-Efficacy Questionnaire, Emotion Regulation Questionnaire, and the Ego-Resiliency Questionnaire. We ran a Confirmatory factor analysis (CFA) on these questionnaires to extract latent variable(s) **Results** A 2-factor CFA out-performed a 1-factor CFA based on scree plot, comparative index, and AIC measures. Factor loadings for factor 1 predominantly represented emotional awareness and monitoring while factor 2 loadings corresponded to emotional regulation and control. We found that awareness and control were unrelated to overall confidence levels in the task. Similarly, the metacognitive ability parameter exhibited a trending but negative association with emotional awareness ($\rho=-0.22$, $p=0.064$) and no significant association with emotional control ($\rho=0.15$, $p=0.212$). **Conclusions** Our results indicate that emotional awareness is a separable construct from emotional control. While neither were significantly correlated with the task-based metacognitive ability parameter, we found a trending association indicating that higher emotional awareness related to worse metacognitive ability. We conclude that self-reported emotional metacognition may not relate to metacognition about risky choice and are running a large replication study to confirm this result.

Disclosures: J.H. Trudeau: None. C. Kao: None. C.E. Haeffner: None. S. Trowbridge: None. S. Lopez-Guzman: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.07/AA10

Topic: I.03. Decision Making

Support: Else Kröner Medical Scientist Kolleg "ClinbrAI: Artificial Intelligence for Clinical Brain Research"

Title: Modelling Hybrid Sequential Biases in the Stop Signal Task: A Longitudinal Analysis using the ABCD study

Authors: *W. WANG^{1,2}, T. KAUFMANN^{2,3,4}, P. DAYAN^{1,2},

¹Computat. Neurosci., Max Planck Inst. for Biol. Cybernetics, Tuebingen, Germany; ²Univ. of Tuebingen, Tuebingen, Germany; ³Univ. of Oslo, Oslo, Norway; ⁴German Ctr. for Mental Hlth. (DZPG), Tuebingen, Germany

Abstract: Many decision-making tasks, including reversal paradigms and the stop signal task (SST), involve blocks of identical trials punctuated by occasional changes or anomalies. To predict the arrival of the latter across trials, decision-makers must balance two forces: Bayesian learning, which progressively favors the conventional, and a hazard function, which often progressively disfavors it. How these forces coexist and interact, leading to adjustments in speed and/or accuracy, remains understudied. Here we introduce a Hybrid Dynamic Bayesian Model (HDBM) of SST performance that parametrizes the two forces, and apply it to reaction time (RT) data from the Adolescent Brain Cognitive Development (ABCD) study. HDBM predicts the probability of a stop trial using two key parameters: α , determining the asymptotic strength of the Bayesian component, and ρ , weighting the hazard function's contribution. The net predictions are expected to be positively correlated with go-trial RTs, as participants become more cautious. We analyzed data from a total of 9,052 participants tested at various combinations of ages 9-10, 11-12, and 13-14. Each completed 360 trials, responding to directional go signals unless a stop signal appeared. As HDBM predicts, as go trials increased (up to 20), RTs initially decreased (Bayesian-driven) and then increased after extended repetitions (hazard-driven). Estimates of α varied widely across participants, whereas ρ generally ranged between 0 and 0.2. In a between-participant analysis, both parameters increased modestly with age. From baseline to 4-year follow-up, α and ρ increased by 0.06 ($p < 0.001$) and 0.016 ($p = 0.008$), based on OLS across three time points ($N = 7268, 5327, 1550$). In a within-participant analysis of the 723 who performed the task on all three occasions, mixed-effects modeling showed larger increases (α : +0.094, $p < 0.001$; ρ : +0.026, $p = 0.013$). ADHD was linked to higher baseline α ($p = 0.017$) and reduced growth ($p < 0.01$), suggesting atypical development. The HDBM, which models across-trial effects, only explained a small (but significant) component of RT variance; fuller explanations arise by using its predictions as initial conditions in a Partially Observable Markov Decision Process (POMDP) of within-trial performance. Our findings suggest that inhibitory control in the SST is influenced by dynamic internal models of sequence structure. The model successfully captures this structure, revealing individual and developmental differences in predictive adaptation. This framework may clarify neural mechanisms of inhibition and aid identification of developmental markers and tools for inhibitory dysfunction.

Disclosures: W. Wang: None. T. Kaufmann: None. P. Dayan: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.08/AA11

Topic: I.03. Decision Making

Support: NIH Grant R01MH121089A

Title: Individual differences in neural correlates of model-based and model-free reinforcement learning computations

Authors: *W. DING¹, J. COCKBURN², J. P. SIMON¹, A. JOHRI¹, S. J. CHO³, S. OH⁴, J. D. FEUSNER⁵, R. TADAYONNEJAD⁶, J. P. O'DOHERTY⁷;

¹Caltech, Pasadena, CA; ²Psychological and Brain Sci., Univ. of Iowa, Iowa City, CA; ³Dept. of Psychology, Univ. of California, Irvine, Santa Monica, CA; ⁴Dept. of Psychology, Univ. of California, Berkeley, Berkeley, CA; ⁵Psychiatry, UCLA Semel Inst. For Neurosci. and Human Behavior, Toronto, ON, Canada; ⁶UCLA, Los Angeles, CA; ⁷California Inst. Technol., Pasadena, CA

Abstract: Two distinct forms of reinforcement learning (RL) have been proposed to account for human action selection under reinforcement: model-free (MF) and model-based (MB). While human behavior on sequential decision-making tasks has long been found to resemble a mixture of these two strategies, little is known about how individual differences in their behavioral expression relate to variation in underlying neural correlates. To address this question, we conducted a large-scale fMRI study in which data were collected from 179 participants performing a variant of the two-step task to distinguish MB and MF neural correlates. Using both strategy-defined subgroups from cluster analyses and computationally-derived parameter estimates, we found that activity in the ventromedial prefrontal cortex (vmPFC) correlated differently with decision value signals from MB and MF learning as a function of individual differences. MB value signals in this region were tightly coupled to the degree to which behavior relied on MB RL. MF value signals, on the other hand, were present in vmPFC irrespective of whether MF RL was directly influencing behavior. We also utilized the large sample size to distinguish MB and MF influences on reward prediction error signals to shed light on a longstanding debate in the field about the extent to which MB computations are reflected in reward prediction errors. We found that reward prediction error activity in the ventral striatum, long thought to be model-free, was in fact best described by an MB strategy, while prediction error signals in a region of the middle caudate were better described as MF. When taken together, these findings provided evidence for the ubiquity of model-free strategies in the brain, even in individuals not actively using a model-free strategy, while providing support for the distinct neural representation of model-based and model-free reward prediction errors. We also examined the individual differences in the encoding of state prediction error (SPE), a model-based RL signature, using a region-of-interest approach. We found that SPEs were encoded in the dorsolateral prefrontal cortex (dlPFC) and intraparietal sulcus (IPS) across individuals using MB, MF, and non-RL strategies, and the encoding strength was modulated by the degree of an individual's MB behavioral expression.

Disclosures: W. Ding: None. J. Cockburn: None. J.P. Simon: None. A. Johri: None. S.J. Cho: None. S. Oh: None. J.D. Feusner: None. R. Tadayonnejad: None. J.P. O'Doherty: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.09/AA12

Topic: I.03. Decision Making

Support: NIH/NINDS Grant 1R34NS132037

Title: Quantifying uncertainty of parameter estimates when applying drift diffusion models to temporally-dependent decision data

Authors: G. RIEGNER¹, *P. REINAGEL², A. SCHWARTZMAN³;

¹Halicioğlu Data Sci. Inst., UCSD, San Diego, CA; ²Neurobio., ³Halicioğlu Data Sci. Inst., UCSD, La Jolla, CA

Abstract: Brain and behavior are in constant flux based on changing internal and external states; consequently, decision behavior is also likely to fluctuate, exhibiting temporal correlations on multiple timescales and/or temporal non-stationarity. The drift diffusion model (DDM) is a ubiquitous parametric model of decision making that describes two-alternative forced-choice (2AFC) decisions as noisy evidence accumulation toward one of two choice boundaries. However, existing methods for fitting the DDM typically assume that: (1) decisions are independent; and (2) parameters are either fixed from decision to decision or drawn i.i.d. from fixed distributions. Moreover, fits to behavioral data commonly report only point estimates. When standard errors are reported, the methods used are subject to these same restrictive assumptions.

To address these limitations, we propose (1) a method to estimate robust standard errors of DDM parameters fit with maximum likelihood, and (2) an application of this method to detect parameter non-stationarity in empirical data using time-windowed estimates. We show that both the parameter and standard error estimators maintain important statistical properties, including consistency and asymptotic normality, even under misspecified conditions, confirming known theory. This enables valid inference of DDM parameters despite misspecification, such as unmodeled parameter variability or temporal correlations between decisions within each estimation time window. In addition, the standard errors are analytic and computationally efficient, unlike resampling or Bayesian methods.

Through parameter recovery simulations, we determine the minimal number of decision trials needed to achieve desired levels of precision under these general conditions. We then applied the method to analyze data from rats in a self-paced 2AFC visual decision task, with hundreds of trials per day collected over many months. Our method allowed us to resolve non-stationary shifts in decision-making parameters across multiple timescales. This work establishes a method for studying dynamic decision processes in naturalistic experiments while relaxing assumptions of correct specification and trial independence, thereby enabling robust statistical inference on decision-making parameters.

Disclosures: G. Riegner: None. P. Reinagel: None. A. Schwartzman: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.10/AA13

Topic: I.03. Decision Making

Support: AP Giannini Foundation
Simons Foundation Grant 441404-AC-80648
U19 NS123716

Title: Understanding decision-making strategies across the lifespan in mice

Authors: *M. B. RYAN^{1,2}, J. ZHOU³, L. YE², A. TARIGHAT², M. VASQUEZ², M. MELIN², J. COUTO², A. K. CHURCHLAND²;
²Neurobio., ³Neurosci., ¹UCLA, Los Angeles, CA

Abstract: Many choices we make on a daily basis are guided by distinct decision-making strategies. Proper arbitration between these strategies is critical for optimal decision-making. However, as we age, our decisions become less flexible, suggesting this balance between decision-making strategies is not static across the lifespan. With age, we tend to make more model-free decisions, which are quick and efficient, but prone to errors as they are made by relying on past outcomes. This is at the expense of model-based decisions, made using an internal model of the environment to predict future outcomes, which offer greater flexibility and accuracy at a higher computational cost. Despite such prominent changes in decision-making with age, the underlying neural mechanisms remain poorly understood. To address this, we first developed a state-space model to classify model-free and model-based decisions in mice performing a reversal learning task across the lifespan (3, 12, 18, and 24 months). Similar to humans, we find that mice show an age-dependent decline in model-based decision-making. What age-related changes in the brain might lead to this bias towards model-free decision-making? Our first step towards answering this question is to understand how these decision-making strategies are represented in the brains of young mice. Previous work suggests that model-free and model-based decisions engage distinct, but highly distributed, corticostriatal circuits. To understand how these circuits might support different decision-making strategies, we performed large-scale in vivo recordings with chronic Neuropixels probes across prefrontal and secondary motor cortices, as well as dorsomedial and dorsolateral striatal subregions in mice during the reversal learning task. We found robust modulation, both in magnitude and timing, of single-unit firing rates between model-free and model-based decisions across these cortical and striatal subregions in young mice. Additionally, we asked whether we could decode the animal's strategy from population level activity. A logistic regression classifier, trained on single-unit activity, accurately predicted trial-by-trial strategy use across the cortex and striatum, independent of choice or reward history. Altogether, this study provides a framework for uncovering different decision-making strategies in mice, both at the behavioral and circuit levels. We are now applying this framework across the lifespan to determine how age-related changes in corticostriatal dynamics contribute to altered decision-making.

Disclosures: M.B. Ryan: None. J. Zhou: None. L. Ye: None. A. Tarighat: None. M. Vasquez: None. M. Melin: None. J. Couto: None. A.K. Churchland: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.11/AA14

Topic: I.03. Decision Making

Title: Computational Markers in Abstinent Smokers Revealed by a Naturalistic Decision-Making Task

Authors: *H. LEE¹, J. JEON⁵, J. LEE², W. SHIM^{6,5,7}, W.-Y. AHN^{2,3,4};

¹Psychology, ²Dept. of Psychology, ³Dept. of Brain and Cognitive Sci., ⁴Interdisciplinary Program in Artificial Intelligence, Seoul Natl. Univ., Seoul, Korea, Republic of; ⁵Dept. of Intelligent Precision Healthcare Convergence, ⁶Biomed. Engin., ⁷Ctr. for Neurosci. Imaging Research, Inst. for Basic Sci., Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Traditional laboratory tasks have commonly served as valuable tools for investigating cognitive mechanisms through structured experimental designs. The multi-armed bandit (MAB) paradigm, widely used to explore decision-making processes involving the explore-exploit trade-off, provides useful insights but typically collects limited behavioral data and simplifies decision contexts by excluding real-world factors like spatial or temporal effort. Understanding how people navigate such costs is crucial, especially in clinical populations where decision biases are linked to maladaptive behaviors like addiction. Although addiction studies show a preference for exploitation, little is known about how this appears in spatially grounded environments. We developed a 3D reinforcement learning task in a Minecraft-based environment, extending the restless MAB paradigm with spatial costs (i.e., distances to rewards) and real-time tracking of locomotion and gaze at 10 Hz. The task captures behavioral signals such as movement entropy, path length, visual entropy, and pitch/yaw variance. To investigate addiction-related differences, we compared non-smokers (N=25), abstinent smokers (N=22), and satiated smokers (N=20), controlling for abstinence duration. Using a hierarchical Bayesian Kalman filter with a softmax rule, we estimated inverse temperature (β) and decay (λ), and tested three cost-sensitive models—linear, hyperbolic, and exponential—each with a cost parameter (γ). We hypothesized stronger group differences in the 3D than 2D task, with abstinent smokers showing greater exploit bias and lower cost sensitivity. We also expected decision type (explore vs. exploit) to interact with locomotion and gaze patterns, reflecting altered behavior in addiction. Supporting this hypothesis, no group differences were found in the 2D task. In the 3D task, abstinent smokers showed higher β , lower λ , and lower γ , suggesting stronger exploit bias, reduced value updating, and lower cost sensitivity. Locomotion and gaze indices confirmed that explore-exploit contrasts were largest in abstinent smokers, reflecting distinct shifts in behavior. Our naturalistic 3D task captured more detailed individual differences than conventional designs. By combining

immersive task design and computational modeling, this approach improves ecological validity and offers a valuable tool for understanding decision-making in addiction.

Disclosures: H. Lee: None. J. Jeon: None. J. Lee: None. W. Shim: None. W. Ahn: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.12/AA15

Topic: I.03. Decision Making

Support: RS-2023-00211018
IBS-R015-D1 (IBS)

Title: Who do you want to team up with? How reward probability and partner support guide decision-making

Authors: *M. SANZ¹, S. JALALI², S. M. YOO³;

¹Ctr. for Neurosci. Imaging CNIR, Suwon-si, Korea, Republic of; ²Ctr. for Neurosci. Imaging Res. (CNIR), Suwon, Korea, Republic of; ³Neurosci., Univ. of Rochester, Minneapolis, MN

Abstract: Traditional behavioral economics and neuroeconomics conceptualize decision-making as a comparison of the expected value of each option. In this framework, the expected value is typically computed as the product of the reward magnitude and the probability of obtaining the reward. However, in real-world settings, the probability of obtaining a reward depends not only on the inherent properties of the option but also on the individual's likelihood of successfully pursuing and acquiring it—a factor formally referred to as affordance, which depends on both one's competence and external support. Hence, the comprehensive model must incorporate not just individual competency, but also collaborative affordances, into the existing formula to compute the outcome accordingly. Here, we investigate whether individuals weigh both collaborative support and reward probability when making decisions in a collective hunting task. In this task, participants (n = 12) used a joystick to hunt moving targets within a 7-second time limit after choosing between two partners. During the pursuit, two partners could slow down the targets when they came within a specific range, thereby facilitating the hunt. Crucially, the presence of each partner enhanced the participant's chances of successfully capturing the target, through partner-specific facilitation and varying levels of assistance. To maximize their reward, participants needed to infer how much each partner improved pursuit success, based on the target's speed reduction, while also considering the partner-specific reward probability (e.g., one partner offered a higher chance of acquiring the reward). We found that participants were sensitive to both the history of reward probability and the variation in partner-specific facilitation that modulated their success during the hunt. To understand how these two factors jointly influence decision-making, we examined whether their effects combined additively or multiplicatively. The results suggest a multiplicative interaction: reward probability scaled the

influence of perceived partner competency, shaping how individuals translated their assessment of partner effectiveness into behavioral commitment under uncertainty.

Disclosures: M. Sanz: None. S. Jalali: None. S.M. Yoo: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.13/AA16

Topic: I.03. Decision Making

Support: Korea Basic Science Institute (National research Facilities and Equipment Center) grant funded by the Ministry of Education (RS-2024- 00435727) National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (RS-2024-00349515, RS-2023-00276729)

Title: Influences of Task Structure on Serial Dependence in Gender Decisions of Human Faces

Authors: *M. S. YEO, S.-H. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Current decisions are often influenced by past ones, a phenomenon known as 'serial dependence.' Researchers have effectively explained serial dependence based on the Bayesian theory of belief updating. This theory posits that decision-makers infer a categorical state of a certain variable from sensory evidence based on an internal model of how sensory evidence is generated while continuously updating their beliefs about the internal model's parameters (e.g., distributions of world states). One important implication of this theory is that the structure of the internal model determines the nature of serial dependence. Here, we verified this implication by comparing serial dependence between two binary decision-making tasks that share the same functional structure for stimulus inputs and response outputs, but differ in the causal structure of their internal models. We examined two tasks: 'relative-state-inference (RSI)' and 'categorical-state-inference (CSI)', which are often used interchangeably to study serial dependence, despite differing causal structures. The RSI task requires decision-makers to determine if a stimulus belongs to the lower or upper half of a distribution, such as sorting coffee beans into 'small' or 'large'. In contrast, the CSI task involves identifying which of two distributions produced the stimulus, like differentiating between Arabica and Robusta coffee beans. In the RSI task, Bayesian belief updating involves revising beliefs about a single distribution post-decision. Conversely, the CSI task requires updating one of two category-conditioned distributions based on the categorical state chosen. This distinction in belief updating suggests that the stimulus-repulsion bias - where current decisions are influenced by previous stimuli - is stronger in the RSI task than in the CSI task. To test our prediction, we had participants perform CSI and RSI tasks on the gender feature of human faces. In the CSI task, they categorized the gender of a facial stimulus, while in the RSI task, they assessed whether a male face appeared less or more

masculine. We utilized deep learning algorithms to generate natural-looking, controllable images that allowed fine modulation of gender representation. Participants were recruited via the online platform Prolific. Consistent with Bayesian theory, the stimulus-repulsion bias was stronger in the RSI task compared to the CSI task. Our findings provide an integrated understanding of probabilistic belief updating and serial dependence in decision-making, emphasizing task structure as a key determinant of serial dependence.

Disclosures: M.S. Yeo: None. S. Lee: None.

Poster

PSTR039: Computational Modeling of Decision-Making and Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR039.14/BB1

Topic: I.03. Decision Making

Support: AFOSR FG23698

Title: A Pilot Study of Computationally-Informed fMRI Decoded Neurofeedback for Modulating Metacognitive Neural Signatures

Authors: *E. OLSSON¹, S. P. ABACHI¹, B. MANISCALCO¹, C. A. CUSHING², M. A. PETERS¹;

¹Cognitive Sci., Univ. of California Irvine, Irvine, CA; ²Psychology, Univ. of California Los Angeles, Los Angeles, CA

Abstract: Metacognitive failures, where confidence misaligns with accuracy, may arise from neural computations described by the Tuned Inhibition (TI) model, which distinguishes roles for less-inhibited (confidence-related) and more-inhibited (decision-related) neural ensembles. This pilot study (N=5) tested if real-time decoded fMRI neurofeedback (DecNef), based on TI model predictions of prefrontal-parietal communication, could train modulation of these patterns and causally influence metacognitive computations.

Subjects completed three DecNef sessions. Neurofeedback (NF) scores, reflecting proximity to target neural patterns, were analyzed using linear mixed-effects models (LME). Pre/post-intervention perceptual (d') and metacognitive (meta- d') sensitivity were assessed via a Random Dot Kinematogram task with confidence ratings, using robust HMeta- d' analysis (Palamedes). Group-level NF scores significantly decreased with practice (LME, $p=0.044$), indicating an average deviation from the intended neural target (where higher scores were better), with variable individual learning. Critically, robust behavioral analysis revealed no significant group-level changes from pre- to post-intervention in d' ($p=0.86$), meta- d' ($p=0.66$), or metacognitive efficiency (M-ratio, $p=0.88$). Initial decoder accuracy and individual NF learning slopes did not significantly correlate with behavioral changes.

This pilot successfully implemented a complex, model-based DecNef paradigm. However, consistent NF signal control towards the target and group-level enhancements in metacognitive

performance were not observed. Findings highlight challenges in translating computational models to effective neurofeedback and underscore needs for refining decoder specificity, feedback strategies, and neural targets. This work informs future model-based neurofeedback research for metacognitive intervention.

Disclosures: E. Olsson: None. S.P. Abachi: None. B. Maniscalco: None. C.A. Cushing: None. M.A. Peters: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.01/BB2

Topic: I.03. Decision Making

Support: NIH Grant 5R01NS104834-04

Title: Structure-function correlations among locus coeruleus norepinephrine neurons

Authors: *Z. SU¹, K. JUNG², P. KOSILLO¹, S. CHEN¹, M. T. SUMMERS¹, A. PIET³, H. HOU², D. FRIEDMANN¹, K. M. HAGIHARA⁸, P. GROTZ⁴, E. HILTON-VANOSDALL¹, M. LEE¹, J. ROHDE¹, J. H. SIEGLE¹, M. RUE⁵, X. CHEN¹, B. R. LEE⁶, K. SVOBODA², Y. ISOGAI¹, J. V. CHANDRASHEKAR¹, J. Y. COHEN⁷;

²Allen Inst. for Neural Dynamics, ³Neurosci., ¹Allen Inst., Seattle, WA; ⁴Allen Inst., SEATTLE, WA; ⁵Barcoded Connectomics, Allen Inst., Des Moines, WA; ⁶Electrophysiology, Allen Inst., Seattle, WA; ⁷Allen Inst., Mercer Island, WA; ⁸Neural Dynamics, Allen Inst. for Neural Dynamics, Friedrich Miescher Inst., Seattle, WA

Abstract: Norepinephrine (NE) is released through most of the central nervous system from the locus coeruleus (LC). LC-NE neurons modulate arousal, attention, and learning. This panoply of functions is often ascribed to broad projections across the brain. However, we have found systematic variation among LC-NE neurons in their projection targets and gene expression pattern.

To test whether LC-NE neurons with different projection targets and gene expression patterns have different functions, we measured action potentials from LC-NE neurons in a behavioral task requiring ongoing learning from decision outcomes. Mice were trained to make choices to lick leftward or rightward for reward with changing probabilities. Because reward probabilities changed over time, they used reward and choice history to make future choices. LC-NE neurons responded differently to decision outcomes. One subset of neurons was excited by RPE while another was excited by lack of reward. The activity of these two populations of neurons correlated with changes in future choices in opposite ways: higher activity in neurons encoding RPE predicted positive changes in policy updates, i.e., increases in the probabilities of rewarded action, consistent with the function of RPE, whereas higher activity in neurons excited by lack of reward predicted negative changes in policy updates.

To determine how LC-NE dynamics correlates with projection targets, we performed two experiments. First, we used antidromic stimulation with collision tests to record electrophysiologically from LC-NE neurons with projections to cortex. Consistent with our anatomical data, these neurons were distributed more dorsally in LC. These cells were excited by RPE, consistent with a role in modulating learning in cortex. Second, we measured axonal calcium dynamics (GCaMP) in LC-NE axons in frontal cortex, cerebellum, and medulla. LC-NE input to frontal cortex correlated with RPE, consistent with the single-neuron measurements. These results reveal a link between the structure and function of a major neuromodulatory system in the brain and show that NE provides a signal for cortex (RPE) to learn from reinforcement.

Disclosures: Z. Su: None. K. Jung: None. P. Kosillo: None. S. Chen: None. M.T. Summers: None. A. Piet: None. H. Hou: None. D. Friedmann: None. K.M. Hagihara: None. P. Grotz: None. E. Hilton-VanOsdall: None. M. Lee: None. J. Rohde: None. J.H. Siegle: None. M. Rue: None. X. Chen: None. B.R. Lee: None. K. Svoboda: None. Y. Isogai: None. J.V. Chandrashekar: None. J.Y. Cohen: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.02/BB3

Topic: I.03. Decision Making

Support: Allen Institute for Neural Dynamics
NIH Grant 5R01MH134833-02

Title: Molecular anatomy of locus coeruleus norepinephrine cells

Authors: P. KOSILLO¹, M. T. SUMMERS¹, S. CHEN¹, Z. SU¹, K. JUNG¹, A. PIET¹, H. HOU¹, D. FRIEDMANN¹, K. M. HAGIHARA¹, P. GROTZ¹, E. HILTON-VANOSDALL¹, M. LEE¹, J. ROHDE¹, M. RUE², O. HO-SHING¹, H. MYERS¹, S. TUGGLE¹, J. H. SIEGLE¹, X. CHEN², B. R. LEE², K. SVOBODA¹, J. Y. COHEN¹, J. V. CHANDRASHEKAR¹, *Y. ISOGAI³;

¹Allen Inst. for Neural Dynamics, ²Allen Inst. for Brain Sci., Allen Inst., Seattle, WA; ³Allen Inst. for Neural Dynamics, Seattle, WA

Abstract: Norepinephrine (NE) is a neuromodulator with a proposed role in multiple cellular and behavioral functions, including plasticity, regulation of intracellular signaling in neuronal and nonneuronal cells, and behavioral states such as arousal, stress, and learning. The locus coeruleus (LC) is one of the principal sources of NE, with LC-NE neurons projecting widely throughout the brain and spinal cord. While our complementary work showed heterogeneity of physiological activities encoding prediction error and reward-related signals in LC-NE cells, the molecular and anatomical basis of LC-NE cell diversity remains largely unknown. Here, we

investigate the structural and molecular organization of LC-NE neurons using multimodal methods to link projection and gene expression: single-neuron reconstructions, BARseq/MAPseq, retrograde tracing, single-nucleus RNA sequencing, MERFISH, and sequencing of retrogradely labeled cells, retroSeq.

First, brain-wide reconstructions of over 100 individual LC-NE neuron morphologies revealed diverse and heterogeneous projections. Notably, soma positions of LC-NE neurons aligned with their targets: neurons projecting to the forebrain are located dorsally, while those targeting the medulla and spinal cord are positioned ventrally. Barcoded connectomics experiments (MAPseq) confirmed these observations.

The organization of LC-NE cells along the dorsoventral axis is also found at the molecular level. Newly sequenced 5,000 LC-NE neurons show a continuous gene expression landscape, aligned with a spatial gene expression gradient found along the dorsoventral axis in previously published MERFISH data (Nardone et al., 2024; PMID: 38438345). With retroSeq, we describe LC-NE neurons in spatial coordinates with forebrain-projecting LC-NE cells expressing ‘dorsal genes’ and spinal cord-projecting cells expressing ‘ventral genes’.

We thus revealed a basic organizational principle of LC-NE cells: projections and gene expression are organized in a single spatial axis. Linking the molecular anatomy, physiology, and behavioral roles of LC-NE cells should further provide a multi-level understanding of the organization of the NE system.

Disclosures: P. Kosillo: None. M.T. Summers: None. S. Chen: None. Z. Su: None. K. Jung: None. A. Piet: None. H. Hou: None. D. Friedmann: None. K.M. Hagihara: None. P. Grotz: None. E. Hilton-VanOsdall: None. M. Lee: None. J. Rohde: None. M. Rue: None. O. Ho-Shing: None. H. Myers: None. S. Tuggle: None. J.H. Siegle: None. X. Chen: None. B.R. Lee: None. K. Svoboda: None. J.Y. Cohen: None. J.V. Chandrashekar: None. Y. Isogai: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.03/BB4

Topic: I.03. Decision Making

Support: NIMH Grant R01MH136230
BBRF NARSAD YI Grant 32856
Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Faculty Fellow Award
NIA Grant R24AG065172
Leon Levy Scholarship in Neuroscience
BBRF NARSAD YI Grant 31140

Title: The ventral tegmental area and dorsal raphe nucleus control neuroeconomically dissociable decision-making algorithms

Authors: B. M. SWEIS^{1,2}, N. JAHAN¹, A. RAMIREZ^{2,1}, E. ANDRAKA^{1,2}, H. L. ROSENBLUM^{2,1}, S. PEDERSEN¹, ***R. DURAND-DE CUTTOLI**²;

¹Psychiatry, ²Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: How the brain makes choices depends on multiple decision-making systems. This includes separable circuits in the brain as well as different roles multiple neuromodulators play in aspects of motivated behavior. Here, we interrogated how multiple regions and neurotransmitter systems, including dopamine and serotonin, contribute to fundamentally distinct types of choices in mice tested on our neuroeconomic foraging paradigm, “Restaurant Row.” On this task, mice have a limited time budget to forage for food by investing in rewards of varying costs (delays, 1-30 s signaled by tone pitch) and subjective value (unique flavors). Each trial was divided into two stages: mice made deliberative accept vs. reject decisions in the offer zone where tones sounded but did not begin counting down until after mice physically entered a separate wait zone where they could make secondary re-evaluative stay vs. quit decisions. In a cohort of 44 Swiss Webster mice, we transfected either the VTA or DRN with adeno-associated viruses expressing either hM3Dq (excitatory, N=11 VTA / 11 DRN), hM4Di (inhibitory, N=10 VTA / 8 DRN), or no chemogenetic receptors (N=4) driven by the synapsin promoter in order to bidirectionally manipulate neural activity in neurons when administered clozapine-N-oxide (CNO) vs. saline via intraperitoneal injection. After animals were well-trained, we compared task performance approximately 30 min following either saline or CNO injections. We found a shift in decision thresholds of willingness to accept offers in the offer zone vs. willingness to wait out delays in the wait zone that depended on (i) the brain region targeted, (ii) the chemogenetic receptor expressed, and (iii) the subjective value of the flavor in pursuit. Inhibition of either the VTA or DRN caused a significant increase in offer zone thresholds with little to no change in wait zone thresholds. Excitatory stimulation of the VTA on the other hand caused a robust decrease in both offer zone and wait zone thresholds. Excitatory stimulation of the DRN caused a striking decrease in only offer zone thresholds with little to no change in wait zone thresholds. On-going efforts are currently characterizing recordings of downstream dopamine and serotonin release using dual-color fiber photometry across 6 brain regions including the medial prefrontal cortex, orbitofrontal cortex, nucleus accumbens, basolateral amygdala, lateral dorsal tegmental area, and interpeduncular nucleus - regions based on a whole-brain activation screen are implicated in functionally distinct but connected roles with VTA vs. DRN during different aspects of neuroeconomic decision-making.

Disclosures: B.M. Sweis: None. N. Jahan: None. A. Ramirez: None. E. Andraka: None. H.L. Rosenblum: None. S. Pedersen: None. R. Durand-De Cuttoli: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.04/BB5

Topic: I.03. Decision Making

Support: NIMH Grant R01MH136230
BBRF NARSAD YI Grant 32856
Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Faculty Fellow Award
NIA Grant R24AG065172
Leon Levy Scholarship in Neuroscience
BBRF NARSAD YI Grant 31140

Title: A novel approach to characterize neuroeconomic foraging decisions underlying social interactions in mice

Authors: *E. ANDRAKA^{1,2}, R. DURAND-DE CUTTOLI¹, D. SCHILLER^{2,1}, B. M. SWEIS^{2,1};
¹Neurosci., ²Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Historically, rodent tasks designed to study the rewarding properties of food and drugs have been instrumental for accessing the neural underpinnings of motivated behaviors. New efforts have repurposed such tasks to explore appetitive social interactions. These approaches have opened doors for integrating behavioral economics with rodent social neuroscience, allowing for the dissociation of computationally distinct decision-making processes along many dimensions of value in a social setting. Here, I adapted the food-based neuroeconomic task, “Restaurant Row”, into a social decision-making task in which mice forage for social interactions rather than food. In this task, isolated mice have 20 minutes to forage for their sole source of social contact with multiple conspecifics who vary in subjective value (social identity based on familiarity and tube test-determined rank). Cost to access social interactions with each conspecific vary in the form of cued delays across trials and task phases. Thus, mice must learn to optimize social decision-making strategies amidst a changing economic landscape. I validated task feasibility under several experimental conditions, including social vs. non-social stimuli, different mouse strains, degrees of sensory contact, social novelty vs. familiarity, housing status, and social hierarchy. Mice discriminate social from non-social (object) targets, as well as novel from familiar social targets, as a function of cued offer costs and more so when physical access to targets is allowed. Further, singly-housed CD1 mice earn more interactions than both C57 and Swiss Webster mice while maintaining stable task engagement across time and different cost epochs. To probe the effects of agentive, reciprocal task engagement on dynamic social behavior, we permitted some mice to forage for the same conspecifics who then on a subsequent session foraged for them in return, while restricting this ability in other mice who instead served only as actors or targets. Actor-target relationships revealed subordinate mice over-selected dominant mice who in turn reciprocally under-selected subordinate mice, a pattern that was not observed with intermediate mice and which may depend on reciprocal access. These findings suggest that identity-related differences in reciprocal interactions reveal important neuroeconomic signatures of social choice that could drive the development of long-term relationships. By strengthening our understanding of long-term social memory, familiarity, and hierarchy dynamics, this approach will help dissect mechanisms of social decision-making that may be altered in psychiatric disorders.

Disclosures: E. Andraka: None. R. Durand-De Cuttoli: None. D. Schiller: None. B.M. Sweis: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.05/BB6

Topic: I.03. Decision Making

Support: NIMH Grant R01MH136230
BBRF NARSAD YI Grant 32856
Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Faculty Fellow Award
NIA Grant R24AG065172
Leon Levy Scholarship in Neuroscience

Title: Validating an abridged training protocol to capture the emergence of neuroeconomic decision-making strategies in mice

Authors: *H. L. ROSENBLUM¹, N. JAHAN², S. PEDERSEN², H. ASHER¹, D. MEDEIROS¹, M. BACON¹, A. BAGGETTA¹, D. J. CAI¹, B. M. SWEIS^{2,1};
¹Neurosci., ²Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Training rodents to perform complex decision-making tasks can take several months. Longitudinal studies such as these are labor and resource intensive, limiting the ability to investigate the progression from naive to expert levels of task performance. This makes it difficult to capture the development of decision-making strategies using in vivo recordings of neural activity. Given the advent of recording methods that can track large populations of single neurons across days, we aimed to establish an approach that could interrogate the neurobiology underlying the formation of complex decision-making strategies in a reasonable timeframe. To address this challenge, we validated an abridged protocol for the neuroeconomic foraging task, Restaurant Row. This task has been used to study processes underlying value-based decision-making across species and models of neuropsychiatric diseases. Notably, our protocol reduced the longitudinal training timeline in mice from over 70 days to under 10 days. On this task, mice have a limited time budget each day to forage for their primary source of food. Mice learned to navigate a square maze in one direction, encountering multiple competing offers for food rewards in serial order. Offers varied in cost (delays ranging from 1-30 s associated with tone pitch) and subjective value (four unique flavors located in spatially separated “restaurants”). Each restaurant contained a T-shaped “offer zone” where mice made initial accept vs. reject decisions based on cued offer costs that, if accepted, advanced to a cued countdown in a separate “wait zone.” Here, rather than progressing through stages of training with costs escalating across weeks as done previously, mice were immediately exposed to the final stage of testing on day 1 with no prior shaping. We tested commonly used strains of mice (C57, CD1, and Swiss Webster) on different session lengths (30 vs. 60 min). We found that all mice were able to acquire the basic structure of the task, learning to increase laps run in the correct direction and total earnings within the first few days of testing. We also found mice learned to use auditory information in the offer zone to skip expensive (high-pitch) offers, a strategy that significantly emerged by day 10 only in C57 and Swiss Webster mice (approximating performance observed by day 70 in our

classic protocols). Our results demonstrate that mice are capable of making cost-informed choices on Restaurant Row within a 10-day timeline. These efforts support the feasibility of experiments aimed at characterizing activity of the same population of cells over a condensed period within which mice develop deliberative decision-making strategies.

Disclosures: H.L. Rosenblum: None. N. Jahan: None. S. Pedersen: None. H. Asher: None. D. Medeiros: None. M. Bacon: None. A. Baggetta: None. D.J. Cai: None. B.M. Sweis: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.06/BB7

Topic: I.03. Decision Making

Support: NIH Grant R01MH131858
Whitehall Foundation Research Grant 2022-12-059
NIH T32 Training in Neurotechnology Translation

Title: Effort-cost transforms emergent patterns of anterior cingulate cortex activity in decision-making

Authors: *T. A. GUPTA¹, S. WILKE², A. Q. KASHAY³;

¹Univ. of California, Los Angeles, CA; ³Biobehavioral Sci., ²UCLA, Los Angeles, CA

Abstract: Effort-based decision-making involves weighing the predicted gains against the costs of exertion and is disrupted in several neuropsychiatric disorders. The anterior cingulate cortex (ACC) is postulated to control such choices based on effort by encoding the value of overcoming effort costs. In a barrier T-Maze assay used to study effort-based decision making in mice, we have shown that optogenetic silencing of ACC neurons disrupts effortful choices under stable conditions (Kashay et al., bioRxiv, 2022). Although these results suggest condition-specific modulation of ACC involvement, the distinct neuronal populations that may facilitate these differential choices in effort-based decision making have not been well-described. The current study utilizes the UCLA miniscope to image calcium activity in individual neurons in the ACC during testing in effort-based decision-making in order to characterize population activity associated with each choice type in effort and no-effort conditions across testing. Mice were injected with gCAMP7f in the ACC and implanted with miniscope GRIN lenses above the injection site. Following surgical recovery, mice were tested in a barrier T-maze in which, on each trial, mice choose between surmounting an effortful obstacle (climbing a barrier) for a high reward (HR) or taking a direct path to a low reward (LR). Calcium signals were extracted using the Minian miniscope analysis pipeline (Dong et al., eLife, 2022). Behavioral events on each trial were aligned to neural activity using the BehaviorDEPOT open-source classifier (Gabriel et al., eLife, 2022). Results indicate that presence of an effort-cost leads to a reduction in the

proportion of ACC neurons that are exclusively excited by high-reward (HR) events, as well as a lower excitation-to-suppression ratio among event-responsive cells. Importantly, these changes occur without altering the overall proportions of modulated neurons, suggesting a shift in selectivity rather than the magnitude of ACC responses. Analysis of ensemble overlap reveals that effort cost diversifies the ACC populations engaged within HR trials and increases the separation between the neuronal ensembles activated during HR and LR trials, indicating more distinct encoding trial behaviors. Furthermore, effort-cost facilitates enhanced decoding of choice from pre-choice neural activity. These findings support a model in which HR choices recruit selective ACC ensembles that encode the value of exerting effort for a larger reward. Direct inhibition of ACC activity may disrupt this selective encoding, leading to impaired effort-cost tradeoff computation and decreased HR choice execution.

Disclosures: T.A. Gupta: None. S. Wilke: None. A.Q. Kashay: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.07/BB8

Topic: I.03. Decision Making

Support: Shanghai Pilot Program for Basic Research – Chinese Academy of Science, Shanghai Branch Grant No. JCYJ-SHFY-2022-011
Shanghai Municipal Science and Technology Major Project
2021SHZDZX

Title: Distributed neuronal computations for value-based decision-making

Authors: *Y. GAO¹, B. ZHANG², Y. PAN³, N. XU⁴;

¹Sino-Danish College, Univ. of Chinese Acad. of Sci., Shanghai, China; ²MIT, McGovern Inst. for Brain Res. at MIT, Cambridge, MA; ³Janelia research campus, Howard Hughes Med. Inst. (HHMI), Ashburn, China; ⁴Chinese Acad. of Sci., Shanghai, China

Abstract: Value-based decision-making requires transforming expected outcomes into actions through coordinated computation across brain networks. While it has been shown that certain brain regions, including orbitofrontal cortex and ventral striatum, encode value information, how these regions represent, compare, and transmit choice information to guide action remains unresolved. We developed an auditory-guided value-based decision-making task in head-fixed mice, in which animals selected between auditory stimuli associated with different reward magnitudes. Using fiber photometry, we found that lateral OFC (lOFC) activity encoded absolute value with temporal dynamics that shifted earlier in the trial (from post-reward to post-stimuli onset) as learning progressed. Furthermore, serotonergic signals in lOFC were modulated by choice outcomes, implicating neuromodulatory mechanisms in updating value representations. To resolve distributed neuronal computations, we recorded from 5,369 units across 26 brain

regions using Neuropixels in expert mice. Single-unit analyses in IOFC revealed encoding of value difference, optimal value location, and choice-related contextual variables including reward history and chosen value. Crucially, optogenetic inhibition of bilateral IOFC impaired task performance, confirming its necessity in value-based decisions. Preliminary single-unit analysis across other brain regions including auditory cortex, secondary motor cortex, dorsal and ventral striatum, hippocampus, and thalamus - revealed encoding of value difference, chosen value and choice signals beyond the OFC. Together, these results support a distributed neural architecture underlying value-based decision-making, anchored by causally essential role of IOFC. Future work will focus on mapping the directionality and temporal structure of value information flow between these regions.

Disclosures: Y. Gao: None. B. zhang: None. Y. Pan: None. N. Xu: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.08/BB9

Topic: I.03. Decision Making

Support: NIMH Grant R01MH136230
BBRF NARSAD YI Grant 32856
Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Faculty Fellow Award
NIA Grant R24AG065172
Leon Levy Scholarship in Neuroscience

Title: Developing a neuroeconomic approach to study altruistic decision-making in mice

Authors: *A. N. RAMIREZ^{1,2}, B. M. SWEIS^{1,2};

¹Neurosci., ²Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Altruistic behaviors benefit another at a cost to oneself. Recent studies have reported a variety of prosocial behaviors in rodents, from comforting and helping behaviors to sharing of resources. To date, the neural computations underlying cost-benefit decision processes when considering the needs of another remains underexplored in rodent models.

We developed a novel social variant of the established Restaurant Row task. An “actor” mouse forages for food rewards at four spatially distinct zones (called “restaurants”). Depending on the restaurant, the actor has the opportunity to feed only itself or both itself and a “recipient” mouse confined in the center of the arena. We used cohoused dyads (n = 6 male dyads) and randomly assigned half to either opaque or mesh center walls containing the recipient (n = 3 dyads/group). This allowed us to assess the effects of access to social information (visual & physical contact) on prosocial choice behavior. Lastly, one restaurant of each of these delivery conditions provided a highly palatable flavor while the other provided a plain flavored pellet. Together, this allowed

us to examine dimensions of subjective value and willingness to be altruistic. Preliminary results revealed that actor mice were able to perform this variant of the Restaurant Row task regardless of the divider type, resembling previously published data. We found that mice with social access in the mesh divider group shifted preferences toward less preferred flavors compared to their opaque divider counterparts. Upon closer look, this was due to an adjustment in foraging strategies: actor mice with social access detracted time away from their preferred flavor that fed only themselves, reallocated toward earning more rewards of their less preferred flavor that instead fed both mice. We then measured choice reaction times in each restaurant's T-shaped intersection from offer onset until the actor made either a skip or enter decision. Compared to the opaque group, actor mice in the mesh group displayed slower reaction times when deciding to skip offers, particularly in less preferred restaurants that fed both mice. Differences in these reaction time metrics, which can capture elements of choice conflict, indicate that mice in the mesh group spent more time deliberating in a restaurant-specific manner. Together, these data highlight that both social access and subjective value influence decisions that involve the consideration of the needs of others. These results suggest mice are capable of modulating foraging strategies to benefit a conspecific, with ongoing efforts to fully characterize the neuroeconomic mediators of altruistic decision-making behavior.

Disclosures: A.N. Ramirez: None. B.M. Sweis: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.09/BB10

Topic: I.03. Decision Making

Support: NIMH Grant R01MH136230
BBRF NARSAD YI Grant 32856
Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Faculty Fellow Award
NIA Grant R24AG065172
Leon Levy Scholarship in Neuroscience
BBRF NARSAD YI Grant 31140

Title: Brain-wide reorganization of activity due to cognitive demand during neuroeconomic task engagement

Authors: *B. M. SWEIS^{1,2}, A. V. AUBRY², L. LI^{2,3}, R. DURAND-DE CUTTOLI²;
¹Psychiatry, ²Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; ³Inst. of Biophysics, State Key Lab. of Cognitive Sci. and Mental Hlth., Univ. of the Chinese Acad. of Sci., Beijing, China

Abstract: How the brain makes choices depends on multiple decision-making systems. This includes roles separable circuits in the brain play in aspects of motivation. We explored how whole-brain activation patterns might be associated with engagement of a complex neuroeconomic foraging paradigm, “Restaurant Row.” On this task, mice have a limited time budget to forage for food by investing in rewards of varying costs (delays, 1-30 s signaled by tone pitch) and subjective value (unique flavors). Each trial was divided into two stages: mice made deliberative accept vs. reject decisions in the offer zone followed by secondary re-evaluative stay vs. quit decisions in the wait zone. Here, we characterized the behavior of 40 outbred Swiss Webster mice. After 60 days of testing, mice were time-sacrificed during task engagement in order to perform whole-brain tissue clearing and staining of 275 regions for cFos expression, an activity-dependent biomarker of recent cell activity. This allowed us to capture a snapshot of brain-wide activation patterns compared to a control group of an additional 10 brains that were not engaged on the task prior to tissue extraction. These control animals were equally food-deprived and fed a matched bolus of food rewards prior to tissue extraction. In the control animals that did not undergo task engagement, we found a remarkable organization of correlated brain activation patterns (cFos counts) that revolved around activation of the ventral tegmental area (VTA) and dorsal raphe nucleus (DRN). Firstly, VTA and DRN activation were strongly correlated with each other. What is more, when correlating every other region against either the VTA or DRN, we found a striking pattern of brain-wide associations that positively correlated with both the VTA and DRN in a coordinated fashion (that is, a “meta-correlation” where the more region X was positively correlated with the VTA, the more it was also correlated with the DRN; and, conversely, the more region Y was negatively correlated with the VTA, it was also negatively correlated with the DRN). When compared to the brains of mice that were engaged in our neuroeconomic task and thus had an increased cognitive demand load prior to tissue extraction, this whole-brain association with the VTA and DRN weakened. Interestingly, we found a striking whole-brain association pattern with the medial prefrontal cortex and nucleus accumbens that emerged with task engagement and that was not present in control brains. These data reveal a shift and restructuring in reward-related whole-brain network signatures that depends on cognitive demand and may recruit a more refined involvement of multiple neurotransmitter systems.

Disclosures: B.M. Sweis: None. A.V. Aubry: None. L. Li: None. R. Durand-De Cuttoli: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.10/BB11

Topic: I.03. Decision Making

Support: NIMH Grant R01MH136230
BBRF NARSAD YI Grant 32856
Burroughs Wellcome Fund Career Award for Medical Scientists

Seaver Foundation Faculty Fellow Award
NIA Grant R24AG065172
Leon Levy Scholarship in Neuroscience

Title: Neuroeconomically dissociable decision-making computations are altered by Shank3 haploinsufficiency

Authors: *N. JAHAN¹, S. PEDERSEN², B. R. SHEVLIN², A. RAMIREZ^{2,3}, E. ANDRAKA^{2,3}, R. DURAND-DE CUTTOLI³, J. D. BUXBAUM², B. M. SWEIS^{2,3};
²Psychiatry, ³Neurosci., ¹Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The mechanisms underlying decision-making encompass distinct information processing computations, which can be differentially perturbed within psychiatric conditions. Autism spectrum disorders (ASDs) are characterized by intellectual impairments, altered communication and social interactions, and repetitive behaviors or restricted interests. Phelan-McDermid Syndrome is a rare ASD caused by deletions in the SHANK3 gene, which is critical for maintaining functional synapses. Rodent studies have been limited in their ability to model cognition of these patients, often relying on full knockout-mice to yield stronger behavioral phenotypes. This reduces the translational potential of animal studies, as homozygous SHANK3 deletions are extremely rare or non-viable in humans. We aimed to fill this knowledge gap by robustly characterizing complex decision-making behavior of haploinsufficient mice by leveraging the neuroeconomic foraging paradigm, “Restaurant Row,” which has been translated across species. We longitudinally tested 48 C57BL/6J mice (SHANK3^{+/+} vs SHANK3^{+/-}, male and female) across a changing economic landscape. Mice had 30-min daily to forage for their primary source of food by navigating a maze, weighing opportunities to earn food rewards of varying costs (tone-indicated delays) and subjective value (flavors). We found robust SHANK3^{+/-} phenotypes typified by altered deliberation behaviors during cost-informed decisions that were not explained by overt differences in feeding behavior, motivation, or other types of choices. Fitting our data to a drift-diffusion model revealed striking changes in drift rates sensitivity to offer value. These findings highlight variations to evidence accumulation processes during value-based judgements and provide a translational computational framework to understand decision-making mechanisms underlying altered behavior in neurodevelopmental disorders.

Disclosures: N. Jahan: None. S. Pedersen: None. B.R. Shevlin: None. A. Ramirez: None. E. Andraka: None. R. Durand-De Cuttoli: None. J.D. Buxbaum: None. B.M. Sweis: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.11/BB12

Topic: I.03. Decision Making

Support: Alfred P. Sloan Research Fellowship
Klingenstein-Simons Neuroscience Fellowship
DP2MH126376
NSF CAREER Award
R01MH125571 (CRCNS)
R01MH136272
McKnight Scholars Award

Title: Temporal discounting in striatal dopamine and choice behavior in rats

Authors: *C. E. GOLDEN¹, A. MARTIN¹, C. M. CONSTANTINOPLE²;
²Ctr. for Neural Sci., ¹New York Univ., New York, NY

Abstract: Across species, the subjective value of future rewards is discounted in a hyperbolic manner, where the value of the reward is inversely proportional to its delay and discounted more rapidly for shorter delays. The rate at which rewards are discounted in time varies by individual. How this discount is reflected by dopamine during intertemporal choice remains an open question. To measure individual discount rates in rats, we developed an intertemporal choice task, inspired by Kobayashi and Schultz, 2008 where water-restricted rats chose between a smaller volume of water reward delivered sooner (SS) or a larger reward delivered later (LL). The reward delay of the SS option was always 0.5 s, while the volume varied between 4, 8, 16, 32, or 40 μ l. The LL reward volume was always 40 μ l, but the delay varied between 1, 2, 4, 8, or 16 s. The SS and LL choice combinations were randomly and independently presented in blocks of trials so that all combinations of reward volumes and delays were possible. Each block began with five forced choice trials to communicate the SS and LL options to the rat, followed by 20 free choice trials where the rat could select either option. An equally likely choice of SS and LL implied that the two options were subjectively equivalent, providing a behavioral read-out of the temporally discounted LL value. Rats discounted the value of LL in a hyperbolic manner and the rate at which it was discounted varied over rats. Choice times were faster for shorter LL delays after the delay option was learned during forced choice trials. Preliminary recordings of striatal dopamine with GRAB_{DA} showed reward prediction errors (RPEs) that reflected temporally discounted future reward at the time of LL choice. The dynamics of how this signature evolved over the block varied by striatal region. Optogenetic stimulation of striatal dopamine release at the time of choice biased reward choices in that block. This suggests that heterogenous dopaminergic RPEs in the striatum contribute to how the value of temporally delayed rewards are learned during intertemporal choice.

Disclosures: C.E. Golden: None. A. Martin: None. C.M. Constantinople: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.12/BB13

Topic: I.03. Decision Making

Support: NIH Grant R01MH128746
NIH Grant R03MH120426
NIH Grant R01NS091010

Title: Distinct Cortical Subnetworks for Value Representation in the Retrosplenial Cortex

Authors: *C.-Y. LIN^{1,2}, S. CHEN^{2,3}, K. TAN^{2,3}, A. NGUYEN^{2,4}, T. KOMIYAMA^{1,2,3};
¹UCSD Dept. of Neurosciences, La Jolla, CA; ²Ctr. for Neural Circuits and Behavior,
³Neurobio., ⁴Cognitive Sci., UC San Diego, La Jolla, CA

Abstract: Value-based decision making is integral to the survival of animals, integrating past actions and outcomes into subjective value estimates that guide future decisions. A hallmark of value-based decision-making is the need for stable, persistent value representations in the brain. Recent work has shown that a subset of the neurons in the retrosplenial cortex (RSC) exhibit robust, persistent value encoding. However, the heterogeneity of the RSC neurons and how value signals flow through the RSC circuit remain largely unknown.

To investigate this, we examined the neural correlates and behavioral functions of distinct projection-defined populations and a genetically identified cell type in RSC during value-based decision-making. With two-photon calcium imaging in mice performing a dynamic foraging task, we identified a distinct population of Scnn1a-positive excitatory neurons in RSC that robustly and persistently encoded value signals. In contrast, other RSC projection-defined populations also encoded value but in a less persistent manner. Among these, deep-layer corticostriatal neurons exhibited the strongest value coding, albeit with lower temporal persistence compared to Scnn1a+ neurons.

Preliminary optogenetic experiments targeting these subpopulations revealed that selective silencing of RSC Scnn1a+ neurons disrupted history-dependent decision strategies, suggesting a unique role for this population in sustaining internal value representations. We propose that RSC Scnn1a+ neurons act as a local hub and reservoir for value signals, supporting flexible access by multiple downstream targets involved in value-based behavior.

Disclosures: C. Lin: None. S. Chen: None. K. Tan: None. A. Nguyen: None. T. Komiyama: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.13/BB14

Topic: I.03. Decision Making

Support: T90DA059110

Title: Multiscale neural dynamics in ACA track alternating discrete strategies during mouse perceptual decision making

Authors: *D. PÉREZ-RIVERA, Jr¹, S. SCHIERECK², D. HOCKER³, C. M. CONSTANTINOPLE³, C. SAVIN²;

¹New York Univ. Ctr. For Neural Sci., New York, NY; ³Ctr. for Neural Sci., ²New York Univ., New York, NY

Abstract: Reconciling neural computations with observed behavior is fundamental to understanding brain function, as both are direct readouts of the brain's underlying operations. Many cognitive processes, and their behavioral manifestations such as shifts in decision-making strategies, evolve across multiple timescales. However, conventional neuroanalytic tools often prioritize fast, within-trial neural activity, thereby limiting a comprehensive reconciliation. Here, we introduce a hierarchical Latent Dynamical System (hLDS) designed to extract and partition low-dimensional neural population dynamics into meaningful computations occurring at both rapid (within-trial) and extended (across-trial) timescales. Our findings demonstrate that hLDS provides a powerful framework for this reconciliation. Specifically, when applied to neural recordings from the mouse anterior cingulate area (ACA) during a visual discrimination task—a paradigm where mice are known to alternate between discrete behavioral strategies—the hLDS revealed multi-timescale across-trial latent neural dynamics. These dynamics simultaneously tracked (1) slow cognitive state transitions highly correlated with ongoing task performance metrics, suggestive of neural correlates for underlying engagement or strategy shifts, and (2) faster task-structure-related changes, such as adaptations to stimulus bias blocks. This capacity to uncover distinct, behaviorally relevant neural processes unfolding concurrently across trials underscores the hLDS's utility in linking neural activity to complex, temporally structured behaviors. Collectively, our work establishes the hLDS as an exciting and interpretable framework for dissecting multi-timescale neural dynamics, thereby offering a significant step towards understanding how neural computations give rise to complex cognitive behaviors as they evolve over time.

Disclosures: D. Pérez-Rivera: None. S. Schiereck: None. D. Hocker: None. C.M. Constantinople: None. C. Savin: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.14/BB15

Topic: I.03. Decision Making

Support: Klingenstein-Simons Fellowship Award in Neuroscience
 DP2MH126376
 R01MH125571

McKnight Scholars Award
F32MH132176

Title: Orbitofrontal projections to dorsal striatum update beliefs about inferred contexts.

Authors: ***M. DEMAEGD**¹, C. M. CONSTANTINOPLE², J. SCHINDLER¹, M. ADLER-WACHTER³, C. SAVIN¹;

²Ctr. for Neural Sci., ¹New York Univ., New York, NY; ³Univ. of Washington, Seattle, WA

Abstract: Animals can rapidly adapt their behavior in dynamic environments by making inferences about the underlying statistics governing the world. How animals generate inferences and update their beliefs about the state they are currently experiencing is a critical cognitive process we have yet to understand. Evidence suggests that the orbitofrontal cortex (OFC) is involved in state inference when task contingencies are partially observable and lesioning the OFC impairs animals' ability to update their inferences when state values change. Here, we sought to characterize the role of OFC-striatal projection neurons in inference-based decision-making.

We used retrograde fluorescent tracers to determine whether the OFC projections target specific subregions of the striatum, which are characterized by distinct relationships to behavior. We found that lateral OFC neurons project to the ventral lateral (VS) and dorso-central striatum (DS) with very little overlap.

We then used a combination of optogenetics and electrophysiology to probe these projection-specific OFC neurons while rats performed a value-based decision-making task. Our lab has developed a temporal wagering task in which rats choose to wait for 1 of 5 volumes of water reward, cued by an auditory tone. There is a latent block structure in which the rat experiences blocks of trials with differing reward statistics which vary in their opportunity cost. We have previously found that rats adjust how long they are willing to wait for rewards depending on the latent reward context. Optogenetically activating OFC-DS, but not OFC-VS neurons, significantly reduced how long animals were willing to wait for rewards in low reward contexts. This is consistent with the hypothesis that stimulation biases animals to believe they are in a high block. Computational modeling of behavior additionally supports this hypothesis and makes specific predictions about changes in the dynamics of wait-times at block transition which are observed in the animal data.

By recording from optogenetically-tagged OFC-DS projection neurons we found that they show privileged encoding of reward volume compared to the entire OFC population or OFC-VS neurons. However, there was also heterogeneous volume encoding (both positive and negative value) among these neurons. This heterogeneity provides strong constraints on the potential circuit mechanisms by which reward encoding OFC-DS projection neurons can bias beliefs about reward states. We are testing these potential circuit mechanisms using a combination of optogenetic perturbation and recurrent neural network modelling of the OFC and striatum.

Disclosures: **M. DeMaegd:** None. **C.M. Constantinople:** None. **J. Schindler:** None. **M. Adler-Wachter:** None. **C. Savin:** None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.15/CC1

Topic: I.03. Decision Making

Support: DP2MH126376
R01MH125571

Title: Investigating the role of hippocampal remapping in hidden state inference

Authors: *A. PERKINS, C. M. CONSTANTINOPOLE;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: A key feature of animal behavior is that with experience, individuals can learn about latent structure, such as the systematically changing frequency of rewards at a location. These regularities in the environment (“latent states”) may be probabilistic and only partially observable, yet animals adapt their behavior to them. We hypothesize that hippocampal remapping reflects and supports inference about abstract, latent states of the environment. We have developed a decision-making task that measures how a rat’s subjective valuation of a water reward shifts across hidden states that offer different reward distributions, in which states offer high, low, or mixed amounts of water reward. The reward distributions in each state are partially overlapping, so the blocks are not cued and must be inferred. Preliminary inactivation of dorsal hippocampus with muscimol reduces sensitivity to hidden states, such that wait times for reward across states are collapsed and undifferentiated compared to controls. Manipulating reward delays in a block-specific manner shows heterogeneity in block-specific decisions across rats. Recordings from dorsal hippocampus with chronically implanted Neuropixels probes have yielded recordings from hundreds of single units during behavior. We will present our ongoing analysis of these electrophysiological recordings in the context of a task requiring inference of abstract latent states of the environment.

Disclosures: A. Perkins: None. C.M. Constantinople: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.16/CC2

Topic: I.03. Decision Making

Support: Leon Levy Scholarship in Neuroscience
NIH Grant DP2MH126376
NIH Grant R01MH125571

Title: Amygdala encodes values during hidden state-inference

Authors: *A. RAJAGOPALAN ECHAMBADI, D. H. LEVY, C. M. CONSTANTINOPLE;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Animal survival in dynamic environments often relies on inferring hidden information about the world to flexibly guide decisions. The orbitofrontal cortex (OFC) is thought to be a key region involved in hidden state inference. Computations underlying this cognitive process require the combination of prior beliefs about the state of the world and the value of extant rewards. It remains unclear how such information is made available to the OFC. The well characterized connectivity between the OFC and the Basolateral Amygdala (BLA) offers a potential source of input about reward values. The BLA has been shown to encode the values of rewards and reward-predictive cues in a variety of Pavlovian settings, although evidence is mixed as to whether these representations are state-dependent. Whether the BLA encodes value while animals perform more complex decision-making tasks, and if this information is leveraged for processes like state inference, remain open questions.

To address these questions, we used Neuropixels to record the activity of BLA and OFC neurons in rats performing a temporal wagering task with hidden reward states. We find that around 50% of BLA neurons encode reward-value available on a given trial - both at cue and reward delivery. State information on the other hand is only weakly encoded. Comparing value coding between BLA & OFC across a range of measures, including linear decoders, discriminability metrics, and generalized linear models (GLMs), indicates that BLA encodes value more strongly. Further, using ANOVA to quantify if reward representations were state-dependent, revealed two types of cells in the BLA - a group that encodes state-independent value and a smaller group that encodes both task-state and value. To understand which aspects of this information are made available to OFC, we are currently leveraging opto-tagging approaches to record from OFC-projecting BLA cells. To test how these projections affect behavior, we are optogenetically activating OFC-projectors in behaving rats. Preliminary results find rats exhibit reduced sensitivity to offer values. Altogether our work suggests a role for value representations in the BLA in supporting value-based decisions, and provides insight into the computations underlying state-inference.

Disclosures: A. Rajagopalan Echambadi: None. D.H. Levy: None. C.M. Constantinople: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.17/CC3

Topic: I.03. Decision Making

Support: DP2MH126376
R01MH125571
Leon Levy Scholarship for Neuroscience

Title: Anatomical and representational characterization of basolateral amygdala projections to the orbitofrontal cortex in rats

Authors: *D. H. LEVY¹, A. RAJAGOPALAN ECHAMBADI², C. M. CONSTANTINOPLE²;
¹NYU, New York, NY; ²Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The basolateral amygdala (BLA) is known to play a role in threat- and reward-motivated behaviors through distinct projections to different brain areas. Modern circuit-based methods have found distinct BLA projections to the ventral hippocampus (vHPC), the central amygdala, the nucleus accumbens (NAc), and the prefrontal cortex (PL/IL). Cells that project to different regions have been found to represent distinct aspects of reward value in a range of Pavlovian paradigms. For example, NAc-projectors encode chiefly positive values, while vHPC-projectors respond to both positive and negative values. Previous literature documents a strong relationship between BLA and the orbitofrontal cortex (OFC), but it is unclear if this population is distinct from the other projection classes within the BLA. The OFC is implicated in assigning value to predictive-cues and is thought to leverage value representations to build and update a cognitive map of the world that can be utilized to guide complex behaviors. Understanding the connectivity between the BLA and the OFC could illuminate the computations underlying these processes. Here we seek to determine if BLA projections to the OFC are topologically and functionally distinct from other BLA projections.

First, we aimed to compare the populations of BLA cells projecting to the OFC to those projecting to the NAc and the vHPC using retrograde viruses. We injected AAVrg-CAG-GFP into either the NAc or the vHPC simultaneously with AAVrg-CAG-tdTomato into the OFC. We found that the populations of cells labeled by GFP and tdTomato fluorophores were non-overlapping. In the NAc injection subjects, we additionally observed a distinct spatial localization of these populations. OFC projecting cells were primarily localized in the anterior and lateral region of the BLA, while NAc projecting cells were primarily found at posterior and medial regions of the BLA.

Neural recordings in our lab have revealed the existence of positive and negative value encoding BLA cells in rats performing a complex temporal wagering task with hidden states. We therefore asked if these functional distinctions mapped on to the spatial organization we observed in our anatomical experiments. In agreement with earlier findings, we do not find a segregation of positive versus negative value encoding cells along the AP or ML axes along which we saw the projection specific subpopulations being divided. Going forward we plan to leverage opto-tagging approaches to record from the OFC-projecting BLA subpopulation specifically to characterize their task-related dynamics.

Disclosures: D.H. Levy: None. A. Rajagopalan Echambadi: None. C.M. Constantinople: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.18/CC4

Topic: I.03. Decision Making

Support: This work was supported by grants to S.H.L. from the Institute for Basic Science (IBS-R002-A2).

Title: Flexible representations of outcome history and value in striatum-projecting parietal neurons during deterministic and probabilistic reversal learning

Authors: *S. KIM¹, S.-H. LEE^{2,3};

¹Korea Advanced Inst. of Sci. and Technol. (KAIST), Daejeon, Korea, Republic of; ²Biol. Sci., Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of; ³Ctr. for Synaptic Brain Dysfunctions, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Understanding how previous choices and outcomes interact is crucial for animals to adjust their behaviors according to rules and make flexible decisions during reversal tasks. Recently, it has been shown that neurons in the posterior parietal cortex (PPC) projecting to the dorsomedial striatum (DMS) (PPC->DMS) encode previous choice history and influence current choices during perceptual decision-making tasks. However, the role of these neurons during the reversal of choice-outcome contingencies remains unclear. In this study, we investigated how PPC->DMS neurons represent previous choice-outcome histories, depending on the uncertainty of outcomes following choices. To explore this, we developed reversal two-alternative forced choice (r2AFC) tasks using a T-maze. Mice were trained to make choices based on reward contingencies, which were reversed either deterministically or probabilistically within a session. Although the two tasks showed overall similarity in behavioral properties, subjects more frequently adopted reversal strategies based on previous outcomes—such as win-stay and lose-shift—in the deterministic task. In addition, our Q-learning analysis revealed that the difference in performance improvement following transitions was related to value-independent choice behavior. Next, we used a miniature fluorescent microscope to image calcium activity in PPC->DMS neurons while mice performed the tasks to find how the PPC->DMS neurons encode task-relevant information. A generalized linear model (GLM) was applied to analyze neural activity and identify neurons encoding values and previous history. Interestingly, the fraction of PPC->DMS neurons encoding previous history was higher in the deterministic task and the fraction of value encoding was higher in the probabilistic task compared to each other task. Our findings suggest that the PPC->DMS circuit represents different task-relevant variables upon reward probability and uncertainty.

Disclosures: S. Kim: None. S. Lee: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.19/CC5

Topic: I.03. Decision Making

Support: Whitehall Foundation Research Grant
Brain and Behavior Research Foundation NARSAD Young Investigator Grant
NIH MH137028

Title: An operant foraging task for mice to reveal neural mechanisms of cost-benefit decision making

Authors: C. E. CALZOLANO, N. GROSEK, S. FEI, *J. M. COX;
Northwestern Univ., Chicago, IL

Abstract: Making choices based on expected outcomes is essential for behaviors such as foraging for food or water, which is vital for survival. Typically, foraging requires making sequential decisions about which resources to pursue and which to forgo. These decisions involve integrating information about the benefit of consuming a resource and the cost of obtaining it. However, despite the importance of this behavior, how cost and benefit information are processed in the brain to affect choice remains incompletely understood. To address this, we developed a new task for mice that is inspired by natural foraging decisions and is well-suited to the investigation of the neural circuit mechanisms of these choices. In this task, mice make sequential choices to pursue or reject offers with costs (time they must hold a nose poke) and benefits (reward size) that vary independently across trials. Mice make choices based on both features and are most likely to accept offers with high profitability (defined as reward size/hold time). Additionally, when we vary the value of the foraging environment by changing the rates mice encounter offers, we find that mice modulate their choices even though the cost and benefit of the offers are unchanged. We are now using this task to test a model of the basal ganglia whereby the direct pathway computes information in favor of performing an action (e.g., benefit) while the indirect pathway computes information against performing an action (e.g., cost). We are imaging activity in the two major cell types in the striatum, direct and indirect pathway spiny projection neurons, using genetically encoded calcium indicators and a miniaturized, head mounted single-photon microscope. By independently varying cost, benefit and environmental value, our task provides a powerful context to disentangle how this information is encoded in the brain to regulate foraging behavior.

Disclosures: C.E. Calzolano: None. N. Grosek: None. S. Fei: None. J.M. Cox: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.20/CC6

Topic: I.03. Decision Making

Title: Computations for value and action in direct pathway striatal neurons during flexible behavior in mice

Authors: *L. M. AMARANTE^{1,2}, A. HIGGS², E. ALBRECHT², A. LANGDON², V. A. ALVAREZ²;

²Natl. Inst. of Mental Hlth., ¹NIH, Bethesda, MD

Abstract: To execute adaptive behavior, choices are made and adjusted based on previous outcomes that will maximize reward. Inability to update future actions is often a key feature of neuropsychiatric disorders, especially those exhibiting compulsive behaviors and characterized by perseverative actions that are hard to stop or control. The corticostriatal circuit, formed by projections from the prelimbic cortex to the dorsomedial striatum (DMS), plays a key role in behavioral flexibility by integrating value information and guiding the selection of future actions. However, the specific mechanisms that allow for this computation are unclear and it is not fully understood how value information from prelimbic cortex is transformed into an action plan in striatal neurons. Further unknown is the specific role of direct pathway medium spiny neurons in striosomes (patches), a neurochemical subcompartment that receives prelimbic cortex innervation. The current project investigates the activity of prelimbic cortical projections to DMS and local DMS neurons, specifically direct pathway neurons in patches, during flexible decision-making in mice using in-vivo fiber photometry. Head-fixed mice perform a probabilistic reversal learning task, where they lick to a left or right spout to make choices after an initial “go” cue, and water is probabilistically rewarded on either spout. The probability of reward changes in a block-like manner to assess how mice use previous outcomes to guide future choice. We simultaneously measured local striatal dopamine (using dLight) and calcium activity of D1 patch neurons (using Gcamp8s) in Prodynorphin-cre (Pdyn-cre) and Drd1a-cre mice during the task. Behaviorally, mice improved accuracy late in trial blocks in the task, and learned to choose the high probability spout quickly after a block switch. Photometry measurements of D1 neurons reveal modulated activity based on the animal’s recent reward history and their expectation of obtaining reward. Further, striatal dopamine versus D1 neuron activity have distinctly different activity patterns based on current outcome and recent reward history. We are utilizing behavioral modeling to measure latent variables to correlate with D1 patch neuron activity. Finally, to compare activity from prelimbic projections to DMS, we are comparing the activity of prelimbic cortical projection terminals in DMS during behavior. The findings of this study will aid in understanding the mechanism that guides flexible behaviors and identify specific roles for direct pathway neurons in integrating prefrontal cortex value information into action selection.

Disclosures: L.M. Amarante: None. A. Higgs: None. E. Albrecht: None. A. Langdon: None. V.A. Alvarez: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.21/CC7

Topic: I.03. Decision Making

Support: DFG OT562/2-1

Title: Baseline dopamine in rat prefrontal cortex reflects the opportunity cost of time investment

Authors: *A. LEE^{1,2}, T. OTT^{1,2};

¹Nachwuchsgruppe Decision Circuits, Inst. für Biologie, Humboldt Univ. of Berlin, Berlin, Germany; ²Bernstein Ctr. for Computat. Neurosci. Berlin, Berlin, Germany

Abstract: Many decisions have delayed outcomes and require investing time to reap the benefits. According to normative theories, time investment should be scaled with its opportunity cost and the expected value of outcomes. While phasic dopamine response signals reward prediction error, recent studies have suggested that the slow fluctuation in cortical dopamine may signal this opportunity cost by estimating the local average reward rate. However, it remains unclear whether this signal guides time investment.

Here we recorded cortical dopamine dynamics using fiber photometry and the genetically-encoded dopamine sensor GRAB-DA3h, while rats performed a dynamic foraging task. This task required investing time into choices for earning uncertain and delayed rewards. We applied a Q-learning model with additional forgetting and choice stickiness mechanisms to infer the subjects' trial-by-trial choice values and their local reward rate estimates.

Preliminary results demonstrate that rats adjusted their choices in proportion to the relative frequency of reward, consistent with the reward-maximizing behavior predicted by the matching law. Aligned with normative theories, their time investment scaled with the model-inferred choice values, providing a trial-by-trial behavioral readout of their subjective value. At the same time, the relative dopamine level, measured by the relative fluorescence, prior to the choice in the baseline period best correlated with the rats' local reward rate estimate, but not the chosen choices' values. It also predicted the dynamic adjustment of time investment on top of the choice value. Our results suggest that baseline dopamine in rat prefrontal cortex may encode an internal estimate of the opportunity cost, potentially informing dynamic adjustments in time investment.

Disclosures: A. Lee: None. T. Ott: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.22/CC8

Topic: I.03. Decision Making

Title: Subconscious representation of reward value in dopamine neurons, amygdala and orbitofrontal cortex in the macaque brain

Authors: *O. TOYOSHIMA¹, R. MATSUMOTO², J. KUNIMATSU⁴, M. MATSUMOTO³;

¹Univ. of Tsukuba, Tsukuba-City, Japan; ²Dept. of Biol. Sci., ³Ctr. for the Evolutionary Origins of Human Behavior (EHUB), Kyoto Univ., Inuyama, Japan; ⁴Div. of Biomed. Science, Fac. of Med., Univ. of Tsukuba, Tsukuba, Japan

Abstract: To choose appropriate actions in an environment, it is important to perceive sensory stimuli that are associated with rewards and punishments. However, because the external world contains an overwhelming amount of sensory information, it is impossible to consciously process all of the information. Psychological studies suggest that this information can be processed subconsciously and influence behavior. However, little is known about how this subconscious information is processed in the brain. In this study, we focused on reward value information that is provided by non-perceived, subconscious sensory stimuli, and investigated how this information is represented in the brain of a macaque monkey. We developed a visual discrimination task combined with classical conditioning. A circular stimulus, either with a small missing segment (top or bottom) or intact, was briefly presented as a conditioned stimulus (CS). The location of the missing segment predicted reward or no reward: the top-missing circle was followed by no reward, while the bottom-missing circle was followed by a reward. The intact circle was followed by the reward or no reward with 50% probability. Immediately after the outcome delivery, the monkey was required to discriminate whether the CS had a missing segment. Notably, following the CS presentation, a visual mask stimulus was presented after a variable delay, referred to as “stimulus onset asynchrony” (SOA: 50, 100 or 200 ms). When the SOA was long, the monkey accurately reported the presence of the missing segment (perceived trials). At shorter SOAs, the monkey frequently failed to detect the missing segment and responded as if the intact circle was presented (non-perceived trials). We investigated how single neurons represent the reward information in non-perceived trials. We recorded single-unit activity from the orbitofrontal cortex (OFC), amygdala, and dopamine neurons, well known components in the reward system, and found that dopamine and amygdala neurons, but not OFC neurons, encoded the reward information even in non-perceived trials. The reward modulation in dopamine and amygdala neurons decreased as the SOA became shorter regardless of whether the monkey perceived the CS or not, whereas those in OFC neurons did not change depending on the SOA. The OFC modulation exhibited a binary-like change depending on whether the monkey perceived the CS or not. Our findings suggest a possible hierarchical mechanism by which the brain processes subliminal value information, with subcortical structures encoding such signals even in the absence of conscious perception and with OFC processing them only when they reached a conscious threshold.

Disclosures: O. Toyoshima: None. R. Matsumoto: None. J. Kunitatsu: None. M. Matsumoto: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.23/CC9

Topic: I.03. Decision Making

Support: Moonshot R&D JPMJMS2294

Title: Neural representation of subjective value in the macaque orbitofrontal cortex, stratum, and amygdala

Authors: *M. OGUCHI, J. JIANG, M. OHSAWA, M. SAKAGAMI;
Tamagawa Univ., Machida, Japan

Abstract: Animals make flexible and adaptive behavior by calculating and comparing the value of choice options associated with different rewards. The reward value is not determined solely by the objective characteristics of the external stimulus but is inherently subjective and strongly dependent on the animal's internal state. In macaque studies, reward choice tasks have been used to identify neural activity associated with subjective value in the orbitofrontal cortex (OFC), midbrain dopamine regions, basolateral amygdala, hippocampus, and anterior cingulate cortex (Padoa-schioppa and Asad, 2006; Cai and Padoa-schioppa, 2012; Lak et al., 2013; Stauffer et al., 2014; Jezzi and Padoa-schioppa, 2020; Knudsen and Wallis, 2021; Pastor-Bernier et al., 2021). However, little is known about what role each of these regions plays in the calculation of the subjective value of rewards and how they cooperate to form hierarchical reward circuits. In this study, we aimed to elucidate the hierarchical processing of subjective value in the macaque brain by simultaneously recording neural activity from the OFC-amygdala and OFC-striatum using free-choice and forced-choice tasks involving multiple types of rewards. The two monkeys used in this study showed preferences for reward and stimulus location in terms of choice rate on free-choice trials and reaction time on forced-choice trials, with reward preference explaining choice behavior better than location preference. We estimated and quantified the subjective values of reward and location from choice behavior in free-choice trials and used these values for neural activity analysis. Preliminary analyses using sliding window analysis of variance and generalized linear models revealed that neurons in the amygdala and OFC showed more discriminative responses to reward and location types, respectively. In addition, the percentage of neurons that showed significant value encoding in the amygdala was higher than in the OFC for both reward and location, while the percentage of neurons whose activity was significantly explained by the interaction between reward and location values was higher in the OFC, suggesting that the amygdala and OFC have different roles in the hierarchical processing of subjective values. In the presentation, we will present a detailed comparison of neural activity in the OFC, amygdala, and striatum, as well as functional connectivity analysis between these regions.

Disclosures: M. Oguchi: None. J. Jiang: None. M. Ohsawa: None. M. Sakagami: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.24/CC10

Topic: I.03. Decision Making

Support: Bio&Medical Technology Development program (RS-2025-02263832)
Basic Science Research Program (RS-2024-00339355)

ASTRA program (RS-2024-00436783)
LAMP Program (RS-2023-00301976)

Title: Parallel processing of tactile and visual value information in the primate globus pallidus externa

Authors: *M. KIM, J.-W. LEE, H. F. KIM;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The cortico-basal ganglia circuit exhibits an anatomical funneling structure: information flows from the cortex to the striatum and then to downstream nuclei such as the globus pallidus internus (GPi) and substantia nigra (SNr). Along this pathway, there is a substantial reduction in both the number of neurons and the regional volume, reflecting the brain's funnel-like architecture. This raises the question of how diverse information is processed with progressively fewer neurons. There are three possible information processing strategies: convergent, parallel, or divergent. Interestingly, a recent study (Hwang et al., 2024) identified bimodal value neurons in the putamen (PUT) that encode both tactile and visual value, alongside modality-selective value neurons. This indicates that sensory modality converges and value information extracts at the single-neuron level. Building on this finding, we next investigated how such convergent information is transformed along the funneling architecture, focusing on the external segment of the globus pallidus (GPe), a key downstream target of striatal output in the indirect pathway. We recorded GPe neural activity while monkeys performed tactile and visual value discrimination tasks. Two monkeys consistently responded faster to high-valued stimuli in both tasks, confirming their ability to recognize tactile and visual values. Among 54 task-related neurons, 45 (83%) encoded value information, including 8 tactile-selective (17%), 21 visual-selective (47%), and 16 bimodal neurons (36%). In terms of coding direction, 35 showed positive value-coding (5 tactile (14%), 16 visual (46%), 14 bimodal (40%)), while 10 showed negative value-coding (3 tactile (30%), 5 visual (50%), 2 bimodal (20%)). This suggests that value and modality information is neither fully converged nor strictly segregated in the GPe. The proportion of these neurons is comparable to that in the PUT, implying that two structures similarly process tactile and visual values. This suggests that the sensory value convergence observed in the PUT is preserved in the GPe in parallel form. It is known that the GPe serves as a hub in the indirect pathway and, despite being a downstream structure, appears to retain all information in parallel form. Our results suggest that the brain processes tactile and visual values through both the indirect (GPe) and direct (PUT) pathways to ensure their proper relay to downstream motor output structures such as the GPi and SNr. How such information is further processed in output nuclei will be a subject of our future investigation.

Disclosures: M. Kim: None. J. Lee: None. H.F. Kim: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.25/CC11

Topic: I.03. Decision Making

Title: Shared temporal dynamics of neural encoding of self- and other-benefitting choices in prosocial, but not selfish, individuals

Authors: *A. MAZZA¹, I. MIRLISENNA¹, N. FAGAN², S. W. CHANG², O. DAL MONTE¹;
¹Dept. of Psychology, Univ. of Turin, Turin, Italy; ²Dept. of Psychology, Yale Univ., New Haven, CT

Abstract: Decision-making is a process composed of sequential and overlapping stages, such as options evaluation, choice commitment, reward consumption and value update. In social contexts, one must compute some of these stages also with respect to other individuals where social determinants such as prosocial tendencies can influence the underlying neural computations. For example, self- and other-benefitting neural value signals are thought to overlap in prosocial individuals at the time of reward consumption and value update. Does such overlap also occur during evaluation and commitment? Here, we asked 75 human participants to make social decisions in which they chose whether or not to exert a cognitive effort to allocate a reward to themselves (Self) or another individual (Other) while recording their neural activity using EEG. Behaviorally, participants were generally less inclined to accept Other-benefitting compared to Self-benefitting offers when these involved cognitive effort costs, though there was considerable variability in their willingness to accept the Other-benefitting offers. Based on this, we split our sample into a Prosocial and a Selfish group and used time-resolved multivariate pattern analysis of EEG to test whether and when Self- and Other-related neural computations overlapped. Results showed that cortical patterns encoding Self- and Other-benefitting choices strongly overlapped in the Prosocial but not the Selfish group, both at the time of options evaluation (300 ms following offer presentation) and choice commitment (400 ms before action). Moreover, these neural dynamics evolved in a recurrent fashion: in both groups, the same pattern characterizing early evaluation was reactivated just before choice commitment. Altogether, these results suggest that prosocial tendencies modulate the sharedness of neural value representation for Self and Other welfare, providing novel insights into the precise temporal evolution of neural signals underlying motivated prosocial decisions.

Disclosures: A. Mazza: None. I. Mirlisenna: None. N. Fagan: None. S.W. Chang: None. O. Dal Monte: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.26/CC12

Topic: I.03. Decision Making

Title: Beyond discrete choices: Investigating human metacognition in continuous value-based decisions

Authors: *L. HUANG¹, H.-K. CHUNG², H.-H. LI¹;

¹Dept. of Psychology, The Ohio State Univ., Columbus, OH; ²Econ., Univ. of Zurich, Zurich, Switzerland

Abstract: Humans' decisions are inherently noisy and variable. Therefore, the ability to track the quality and variability of one's own decisions—a form of metacognition—is critical for making better decisions. Previous research on metacognition in value-based decision-making has been limited to discrete choice scenarios, leaving open the important question of how well humans can evaluate the quality of their decisions in continuous valuation contexts. We address this issue by using a value-based estimation task in which participants provide valuations on a continuous scale along with their associated uncertainty. In a behavioral experiment, human participants (N = 18) performed a continuous value estimation task adapted from the Becker-DeGroot-Marschak (BDM) paradigm. Each trial started with the presentation of a snack item on the screen. Participants first reported their willingness-to-pay (WTP). Then, they indicated a WTP range by specifying the minimum and maximum prices they would be willing to pay, providing an explicit measure of perceived valuation uncertainty, with larger ranges reflecting higher uncertainty. 30 snacks were tested, each with four repetitions. To quantify valuation variability, we computed WTP deviation, defined as the absolute difference between each trial-level WTP and the item-level average WTP across repetitions. Linear mixed-effects modeling revealed a significant positive correlation between WTP deviation and reported range, even when controlling for item-specific effects. These results suggest that participants have metacognitive access to trial-by-trial variability in continuous valuation beyond item-specific uncertainty. In a subsequent 2AFC choice task, participants selected their preferred snack from pairs of items they had valued in the estimation task. Choice consistency, defined as selecting the item with a higher item-level WTP, increased with the value difference between the two snacks. However, this effect was attenuated by the averaged valuation uncertainty (WTP range from the estimation task) of the two items, indicating that reported uncertainty captured meaningful inherent item-wise variability and predicted choice behaviors. An ongoing fMRI experiment using the same experimental design will enable us to investigate the neural mechanisms underlying variability and uncertainty in continuous value-based decisions. Together, these findings establish an approach to studying metacognition in valuation and demonstrate that people have metacognitive access to, and can explicitly report, their uncertainty in continuous value-based decisions.

Disclosures: L. Huang: None. H. Chung: None. H. Li: None.

Poster

PSTR040: Neural Mechanisms: Valuation and Decision

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR040.27/CC13

Topic: I.03. Decision Making

Title: A Meta-Analysis of the Influence of Conscious Deliberate and Arbitrary Choices on the Readiness Potential and Its Impact on the Free Will Debate

Authors: *C. POLIZIANI¹, U. MAOZ²;

²Psychology & Brain Inst., ¹Chapman Univ., Orange, CA

Abstract: A Meta-Analysis of the Influence of Conscious Deliberate and Arbitrary Choices on the Readiness Potential and Its Impact on the Free Will Debate

Cristina Poliziani¹, Uri Maoz²

¹Chapman University, Institute for Interdisciplinary Brain and Behavioral Sciences

²Chapman University, Institute for Interdisciplinary Brain and Behavioral Sciences The readiness potential (RP), a slow negative-going EEG signal preceding voluntary movement, has been central to the neuroscience of volition. Landmark studies reported that the RP precedes conscious intention to act, suggesting that voluntary actions may be initiated unconsciously. However, these studies have primarily examined arbitrary decisions, raising questions about whether their conclusions generalize to deliberate choices - those central to debates on free will. Some studies report differences in RP dynamics between arbitrary and deliberate decisions, while others do not. To address this inconsistency, we conducted a comprehensive systematic review and meta-analysis of 41 EEG studies that reported RP waveforms for different volitional tasks. Based on predefined philosophical and methodological criteria, we categorized studies along a continuum of decision types: arbitrary, ambiguous, and deliberate. From each study, we extracted RP onset time, peak negativity, and the time of movement onset directly from published waveforms. We used linear mixed effect models to assess whether RP characteristics differed by decision type or measurement moment, while accounting for sample sizes across papers. No significant effects were found for either condition or timepoint on RP amplitude or latency. Sensitivity analyses confirmed these findings: results were unchanged when excluding studies with positive-going RPs, and computing direct RP amplitude differences between conditions (e.g., deliberate vs. arbitrary) also yielded no significant effects. These results suggest that previously reported differences in RP characteristics across decision types are not robust across the literature. Our findings highlight the need for standardized task categorization and waveform analysis protocols to clarify the neural correlates of volitional decision-making and their implications for theories of free will.

Disclosures: C. Poliziani: None. U. Maoz: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.01/CC14

Topic: I.04. Executive Functions

Support: NSF CAREER BCS-2048066
T32 AG020506

Title: Precision fMRI reveals highly interdigitated network patches with conserved motifs in the individual lateral prefrontal cortex

Authors: ***Z. LADWIG**¹, K. ZENDEHROUH KERMANI⁴, N. R. LABORA⁵, J. HERNANDEZ⁶, M. DORN², R. BRAGA³, C. GRATTON⁷;

¹Northwestern Univ., Chicago, IL; ²Northwestern Univ., Evanston, IL; ³Neurol., Northwestern Univ., Chicago, IL; ⁴Dept. of Psychology, Univ. of Illinois Urbana-Champaign, Urbana, IL;

⁵Univ. of Minnesota, Minneapolis, MN; ⁶Harvard Univ., Cambridge, MA; ⁷Psychology, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Despite its central role in cognition, the functional organization of the lateral prefrontal cortex (LPFC) remains debated. Dominant models emphasize broad, slowly varying gradients of function, often portraying the LPFC as a multifunctional region that flexibly supports cognitive control (Duncan & Owen, 2000; Koechlin et al., 2003; Abdullah et al., 2022; Margulies et al., 2016). But recent precision neuroimaging studies suggest that group-level models may blur or miss finer distinctions, particularly in regions like the LPFC that show high inter-individual variability (Fedorenko et al., 2012; Michalka et al., 2015; DiNicola et al., 2024; Mueller et al., 2013; Seitzman et al., 2019). Here, we set out to comprehensively characterize fine-scale LPFC organization using a precision fMRI dataset from N=10 deeply sampled individuals. Each participant completed two hours of resting-state fMRI and eight hours of task-based fMRI spanning a range of high-level cognitive demands. Individual-level network maps revealed a striking degree of patchiness and interdigitation among distinct network regions supporting different functions. Compared to group-level estimates, we observed less dominance of the frontoparietal network and a higher density of network borders—especially in anterior LPFC. While the exact network positions varied across individuals, several conserved spatial motifs emerged, alongside clearly idiosyncratic features. These patterns were consistent across multiple analytic approaches, providing strong evidence that the LPFC contains fine-grained, functionally distinct subregions not captured by traditional models. Our findings suggest that the LPFC may be a uniquely dense zone of network topography, and underscore the importance of individual-level analyses for both basic and translational neuroscience.

Disclosures: Z. Ladwig: None. K. Zendehrouh Kermani: None. N.R. Labora: None. J. Hernandez: None. M. Dorn: None. R. Braga: None. C. Gratton: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.02/CC15

Topic: I.04. Executive Functions

Title: Interdigitated regions of human prefrontal cortex reflect distinct medial temporal lobe connections and cognitive specializations

Authors: *R. BRAGA¹, D. EDMONDS³, J. SALVO², N. L. ANDERSON⁴;

¹Northwestern Univ., Chicago, IL; ²Northwestern Univ., Evanston, IL; ³Northwestern Univ. Interdepartmental Neurosci. Program, Chicago, IL; ⁴Neurol., Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL

Abstract: The prefrontal cortex (PFC) supports diverse aspects of higher cognition, yet functional zones within PFC are often spatially interdigitated, raising questions about how such fine-scale organization arises and how it relates to large-scale brain networks. Here, we leverage individualized precision fMRI to investigate how medial temporal lobe (MTL) connectivity helps shape the organization of functional networks within the human inferior frontal cortex (IFC). Specifically, we focus on two networks: (1) Default Network-B (DN-B), linked to anterior MTL structures including the amygdala, and (2) the core language (LANG) network, which is recruited during language comprehension.

We show that DN-B and LANG occupy interdigitated zones within lateral PFC, particularly along the IFC. Despite this close juxtaposition and interdigitation, DN-B is functionally connected to the amygdala and selectively recruited during tasks involving social inference and emotional pain (e.g., theory of mind and empathy contrasts), while the LANG network is functionally distinct—unrelated to amygdala connectivity—and recruited during both written and spoken language tasks. Across eight individuals, we demonstrate that these two networks can be reliably identified and distinguished within the same participants using both resting-state functional connectivity and multiple task contrasts per domain (e.g., two language tasks, two social cognition tasks), confirming the robustness of their spatial and functional dissociation. These findings suggest that long-range connectivity with evolutionarily conserved limbic structures underlies the specialization of adjacent cortical networks in human PFC. Moreover, this work highlights how individualized network mapping can delineate important distinctions within PFC, offering new insights into the organization of human cognition.

Disclosures: R. Braga: None. D. Edmonds: None. J. Salvo: None. N.L. Anderson: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.03/DD1

Topic: I.04. Executive Functions

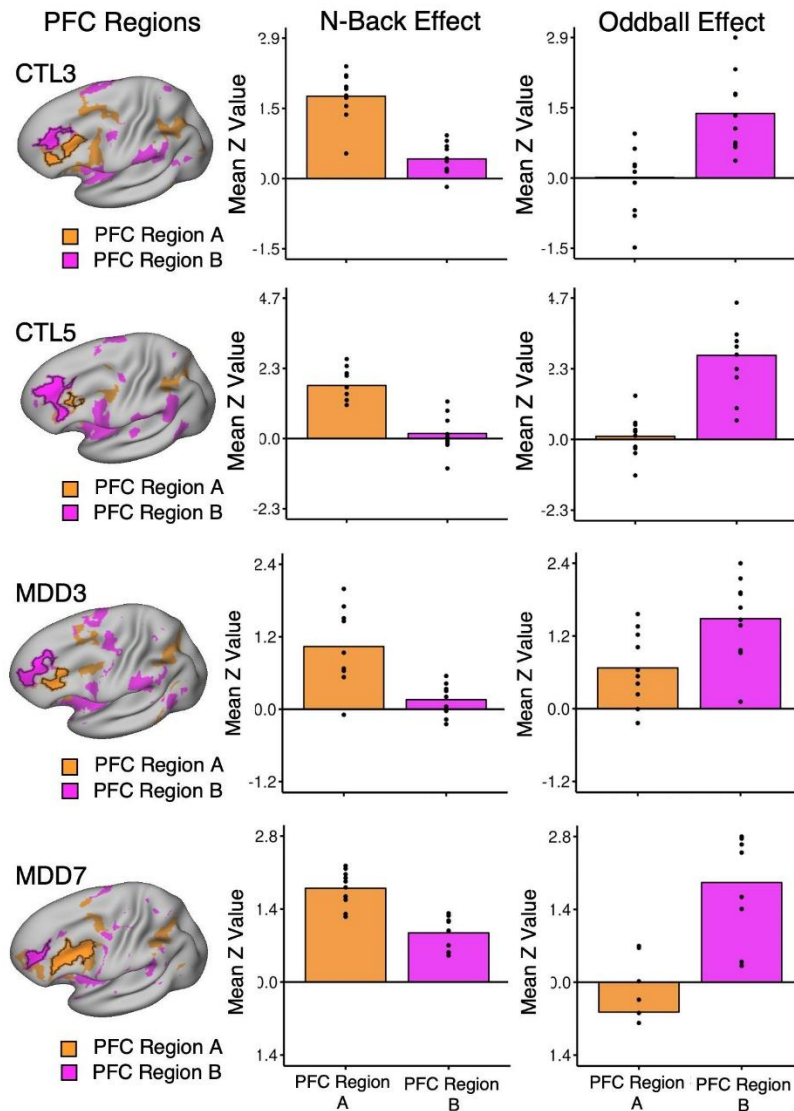
Support: 5R01MH129367-02
MH124004
P50MH106435
S10OD020039

Title: Side-by-side regions in dorsolateral prefrontal cortex robustly dissociate salience and working memory

Authors: *A. BILLOT^{1,3}, W. SUN⁴, K. RODRIGUES¹, X. WEI⁴, M. ELDAIEF², R. L. BUCKNER⁵;

²Neurol. and Psychiatry, ¹Massachusetts Gen. Hosp., Charlestown, MA; ³Harvard Med. Sch., Boston, MA; ⁵Psychology and Ctr. for Brain Sci., ⁴Harvard Univ., Cambridge, MA

Abstract: Dorsolateral prefrontal cortex (DLPFC) is implicated in top-down cognitive control and working memory. Recently, a specific region of DLPFC that is anatomically adjacent to regions implicated in cognitive control was discovered to be coupled to ventral portions of the striatum. We isolated this DLPFC region in 14 highly sampled individuals (18-34 years old, 9 women) using precision MRI (N = 15-24 resting-state runs) and found that it robustly responds to salient targets in an oddball detection task and can be dissociated from adjacent regions that respond to working memory demands. In a replication study in 10 additional participants (24-39 years old, 4 women), we identified the two side-by-side DLPFC regions from a single MRI session using functional connectivity and then tested functional response properties across 10 within-individual prospective task fMRI sessions. In every individual, the distinct juxtaposed regions of DLPFC could be double dissociated, with one region responding strongly to the working memory task and minimally to the oddball detection task and the other region showing the opposite pattern. Figure 1 presents the functional double dissociation in adjacent DLPFC regions in 4 example individuals (interaction between DLPFC region and task effect: $p < 0.001$ for each individual). DLPFC is heterogeneous with anatomically and functionally distinct regions near to one another that gain their specialized functional response properties from the brain-wide networks in which they are embedded. Of interest, the DLPFC region we identified as responding to salient/transient events is likely the neuromodulatory target for the treatment of Major Depressive Disorder (MDD) in most individuals, further supporting its putative functional specialization.



Disclosures: A. Billot: None. W. Sun: None. K. Rodrigues: None. X. Wei: None. M. Eldaief: None. R.L. Buckner: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.05/DD3

Topic: I.04. Executive Functions

Support: ONR MURI N00014-19-12332
BRIDGE Center Seed Grant

Title: What do auditory regions of prefrontal cortex do? fMRI evidence across multiple tasks

Authors: *A. L. NOYCE¹, W. LIANG¹, S. LUTHRA³, B. SHINN-CUNNINGHAM²;
²Neurosci. Inst., ¹Carnegie Mellon Univ., Pittsburgh, PA; ³Stony Brook Univ., Stony Brook, NY

Abstract: The organization of prefrontal cortex (PFC) is multifaceted and complex. Our prior work has identified at least five bilateral regions within PFC that robustly prefer auditory (over visual) cognition (Noyce 2022). While many of these regions fall within the frontoparietal control network, their precise contributions to cognition are not well understood, and their functional specializations remain disputed. Here, we attempt to reconcile these findings by collecting fMRI measurements of multiple tasks in the same individual subjects, yielding a multidimensional functional profile for each brain structure of interest. Our tasks include Reading (to activate language processing), Auditory and Visual 2-Back (to identify sensory-biased structures), Auditory Spatial and Nonspatial Memory (to explore representations of specific features), and Tonotopy (to identify any selectivity for acoustic frequency). After preprocessing, Tonotopy data is analyzed with a phase-encoding analysis; all other tasks are analyzed with GLM fits. In our first analysis, the Auditory and Visual 2-Back data is used to draw sensory-biased region of interest labels in individual subjects; all other task data is used to characterize the response of those regions. Our preliminary data (N=17) suggests that language activity is left-localized (unlike the bilateral auditory network) and restricted to a subset of the auditory network. Auditory recruitment for working memory is strongest along the precentral sulcus and weaker for opercular regions, but does not vary with feature (spatial vs. nonspatial) or with the quality of the sensory input (spatialization cue). No regions of PFC exhibit tonotopic selectivity. Secondary analyses include comparing ROIs drawn from the 2-Back task to ROIs drawn from the others, identifying patterns of adjacency and overlap, and relating PFC functional specialization to its long-range network connectivity. These results clarify the mechanisms by which PFC adaptively adjusts neural computations, guiding flexible behavior in the face of changing task demands.

Disclosures: A.L. Noyce: None. W. Liang: None. S. Luthra: None. B. Shinn-Cunningham: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.06/DD4

Topic: I.04. Executive Functions

Support: NSF grant BCS-1829394 to D.C.S

Title: Dynamic task-based reorganization of sensory-biased and supramodal working memory networks in the human cerebral cortex

Authors: ***T. POSSIDENTE**¹, V. TRIPATHI², J. T. MCGUIRE¹, D. C. SOMERS¹;
¹Psychological & Brain Sci., Boston Univ., Boston, MA; ²Cognitive and Brain Sci., IIT
Gandhinagar, Gandhinagar, India

Abstract: Sensory working memory (WM) is supported by a distributed set of brain regions. Visual working memory and auditory working memory recruit different networks, which include multiple sensory-biased regions interleaved across frontal cortex and traditional posterior sensory cortices. Additionally, a fronto-parietal network of supramodal multiple-demand regions is well recruited by sensory working memory in both modalities. Here we examined functional connectivity between visual-biased, auditory-biased, and supramodal WM networks by collecting fMRI data from 24 human participants (aged 18-43; 11 men and 13 women [self-identified]). Resting-state fMRI (N=18) revealed that the visual-biased WM network exhibits stronger functional connectivity with supramodal regions than does the auditory-biased WM network. This finding replicates prior work from our laboratory (Tobyne et al., 2018; Noyce et al., 2022) and points to a potential functional asymmetry between visual and auditory WM mechanisms; visual cognition may have preferred access to supramodal WM brain structures. Therefore, we hypothesized that visual and auditory WM task performance would evoke asymmetric changes in functional connectivity between visual-biased, auditory-biased, and supramodal networks. To test this hypothesis, we examined changes in functional connectivity that occur when participants perform visual or auditory WM tasks (N=21). Stair-casing procedures were employed to equate task difficulty across sensory modalities and to rule out task difficulty as explanation of network changes. Significant task-based network reorganization was observed and was driven primarily by the auditory WM task. Auditory WM produced substantial network changes that increased the access of the auditory-biased network to the supramodal network: auditory connectivity to supramodal regions and to visual-biased frontal regions increased, while connectivity from posterior visual areas to supramodal and frontal visual regions decreased. In contrast, the visual task produced minimal changes in functional connectivity. Moreover, increased strength of auditory-biased network connectivity changes predicted increased subject behavioral performance on the auditory task. Therefore, the visual WM network appears to have privileged access to supramodal WM cortical structures at rest, but dynamic network changes permit auditory WM to gain the necessary access to the supramodal network. This study reveals new insights into the functional organization of the frontal cortex, examines how this organization dynamically facilitates WM tasks, and connects these changes to behavior.

Disclosures: **T. Possidente:** None. **V. Tripathi:** None. **J.T. McGuire:** None. **D.C. Somers:** None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.07/DD5

Topic: I.04. Executive Functions

Support: NSF grant BCS-1829394
NSF grant BCS-1625552

Title: Visual and auditory working memory maintenance in sensory-biased and supramodal frontal and posterior cortex

Authors: D. BEELER¹, V. TRIPATHI², T. POSSIDENTE¹, *D. C. SOMERS¹;

¹Psychological & Brain Sci., Boston Univ., Boston, MA; ²Dept. of Cognitive and Brain Sci., IIT Gandhinagar, Gandhinagar, India

Abstract: Visual and auditory working memory (WM) tasks recruit multiple regions in human frontal and posterior cortex, including sensory-biased (SB) regions that prefer one sensory modality and supramodal (SM) areas that respond equally strongly for either modality. Here, we isolated WM-specific processing in each of these areas by examining elevated activity and stimulus-specific representations during the maintenance phase of WM. During fMRI scans, subjects (N=16; 9 male; aged 18-42) performed retro-cued, long-delay working memory tasks with visual and auditory stimuli. On each trial two stimuli of the same modality, but of different frequencies (visual: Gabor spatial frequency; auditory: tone frequency) were presented sequentially, followed by a cue indicating which of the two stimuli to maintain in WM, or to hold or drop both in WM. After an 8-s maintenance period, subjects reported whether the frequency of a probe stimulus was higher/lower than the WM stimulus. Staircasing procedures ensured that subjects maintained high-precision WM representations and that task difficulty was equated. A separate 2-back WM task was used to define ROIs. All frontal and posterior SB ROIs exhibited stronger activity for their preferred modality during WM encoding, but only frontal regions exhibited this preference during the critical WM maintenance phase. Frontal visual-biased regions sPCS and iPCS exhibited significantly greater delay-period activity for hold vs. drop trials for visual but not auditory stimuli. Conversely, frontal auditory-biased regions tgPCS and cmSFG exhibited significantly greater delay-period activity (hold vs. drop) for auditory but not visual stimuli. MVPA revealed that the contents of visual WM could be decoded from visual-biased frontal and posterior regions, but not from auditory regions. The contents of auditory WM could be decoded from auditory-biased frontal and posterior regions and from visual-biased frontal, but not posterior regions. This observation is consistent with prior reports of some supramodal WM function in visual-, but not auditory-biased frontal regions. SM frontal regions aINS and preSMA exhibited greater hold vs. drop activity in both modalities, but the contents of WM could not be decoded reliably for either modality. In summary, SM frontal regions supported elevated delay period activity without stimulus-specific information and posterior SB regions held stimulus-specific WM representations without significant elevation of activity. Frontal SB regions supported both elevated activity and stimulus specific representations during WM maintenance, suggesting that these regions serve central roles in sensory WM.

Disclosures: D. Beeler: None. V. Tripathi: None. T. Possidente: None. D.C. Somers: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.08/DD6

Topic: I.04. Executive Functions

Support: NIH Grant R01EY031589
NIH Grant U01EY025858
Evelyn F. McKnight Brain Research Foundation

Title: A region within the orbitofrontal cortex connects to where the attention is

Authors: *K. M. VISSCHER¹, P. DEMIRAYAK², S. NOLIN¹, P. STEWART³, M. DEFENDERFER⁴, L. L. FLEMING⁵;

¹Univ. of Alabama, Birmingham, Birmingham, AL; ²Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; ³Univ. of Alabama, Birmingham, Homewood, AL; ⁴Grad. Biomed. Sci., Univ. of Alabama At Birmingham, Calera, AL; ⁵Psychiatry, Mclean Hosp./Harvard Med. Sch., Atlanta, GA

Abstract: The human prefrontal cortex is a complex, fine-grained mosaic of interdigitated circuits critical for different aspects of cognition. Here we show evidence from three separate studies implicating the same subregion of the orbitofrontal cortex as having stronger connections to attended cortical areas. Using data from participants performing a task with simultaneous auditory and visual stimuli, we show that this orbitofrontal region is more strongly functionally connected to auditory cortical regions when the auditory stimulus is attended, and to visual cortical regions when the visual stimulus is attended. During rest, this same region showed stronger functional connections to V1 representations of central vision compared to peripheral vision. That is, it is more strongly connected to representations of the part of vision we use for daily tasks that require attention. We reproduced this effect in two separate datasets. Finally, consistent with these functional connections, this orbitofrontal cortex region also showed stronger structural connections to central versus peripheral V1 representations, as examined using the Human Connectome Project dataset. Thus, this portion of the orbitofrontal cortex exhibits preferential functional and structural connections to brain regions processing attended stimuli, and flexibly modifies its connections based on task demands. These findings highlight this OFC subregion's importance for flexible attentional control, advancing our understanding of fine-grained PFC organization.

Disclosures: K.M. Visscher: None. P. Demirayak: None. S. Nolin: None. P. Stewart: None. M. Defenderfer: None. L.L. Fleming: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.09/DD7

Topic: I.04. Executive Functions

Support: UE5NS070680-15
U24NS109103-07
UH3NS123310-01A1
R01MH122431-04
R01NS021135-35

Title: An orbitofrontal microcircuit for approach-avoidance decision-making

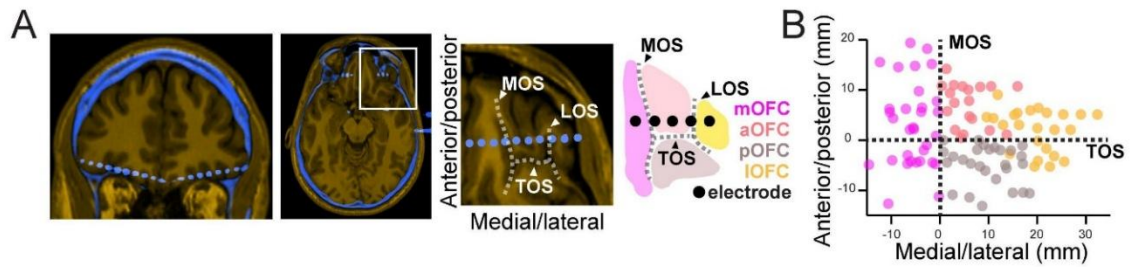
Authors: *C. K. STARKWEATHER¹, E. H. WILLBRAND³, K. K. SELLERS⁴, P. HULLETT², A. KRYSTAL⁵, K. S. WEINER⁷, J. T. WILLIE⁸, P. BRUNNER⁹, M. HSU¹⁰, E. F. CHANG⁶, R. T. KNIGHT¹¹;

¹Neurolog. Surgery, ²Bioengineering, Univ. of California San Francisco, San Francisco, CA; ³Sch. of Med. and Publ. Hlth., Univ. of Wisconsin-Madison, Madison, WI; ⁴Neurolog. Surgery, UCSF, San Francisco, CA; ⁵Dept. of Psychiatry, ⁶Neurolog. Surgery, Univ. of California, San Francisco, San Francisco, CA; ⁷Psychology, Univ. of California, Berkeley, Berkeley, CA; ⁸Neurolog. Surgery, Washington Univ. Sch. of Med., Saint Louis, MO; ⁹Dept. of Neurosurg., Washington Univ., St. Louis, MO; ¹⁰Haas Sch. of Business, ¹¹Psychology and Neurosci., UC Berkeley, Berkeley, CA

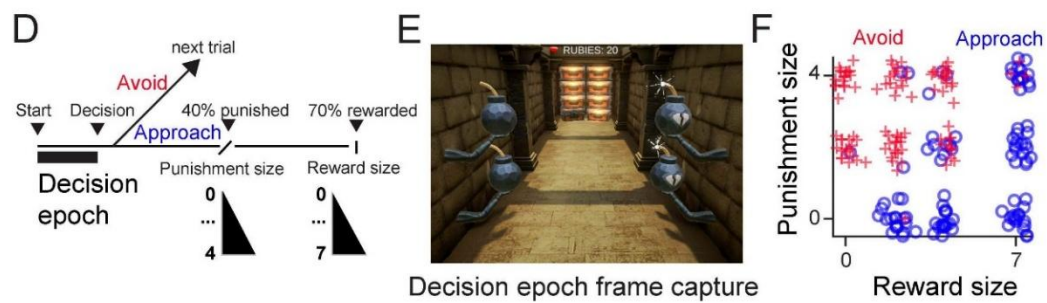
Abstract: A hungry traveler could explore a bustling market for a delicious meal—risking pickpocketing—or stay at her quiet hotel for dinner. This decision is an example of approach-avoidance, a conflict in which approaching a reward also carries potential punishment. The orbitofrontal cortex (OFC) is proposed to arbitrate approach-avoidance decisions, yet little is known about the real-time computations within OFC during these decisions. Here we uncovered two anatomically separated signals within the OFC that displayed increased and decreased activity prior to approach, in medial and lateral compartments of OFC, respectively. Prior to decisions, these signals rapidly alternated between discrete pro-approach and pro-avoidant states in a circuit invoking mutual inhibition, thus introducing a new functional architecture of the human OFC during decision-making. We implemented a formal computational model of this circuit revealing discrete attractor dynamics sensitive to decision conflict, concordant with neural data.

Method

Intracranial recordings covered a wide swathe of OFC anatomy:

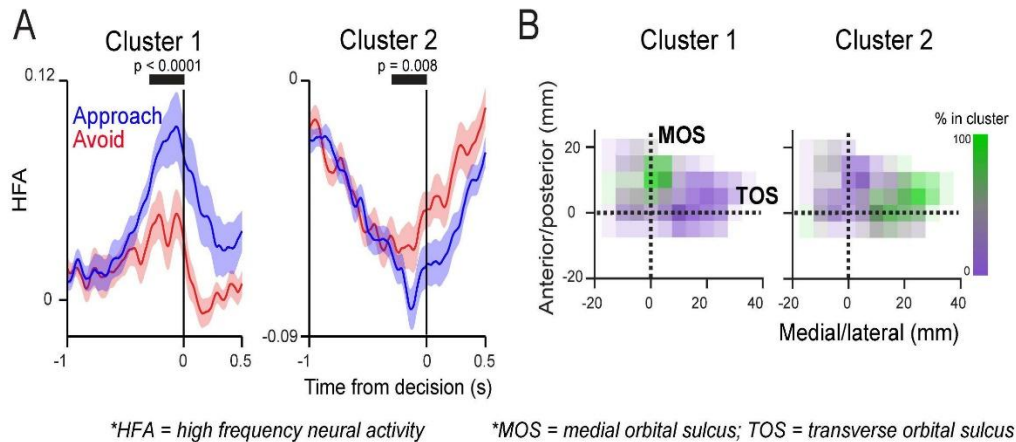


Implanted patients performed a videogame-style approach-avoidance task:

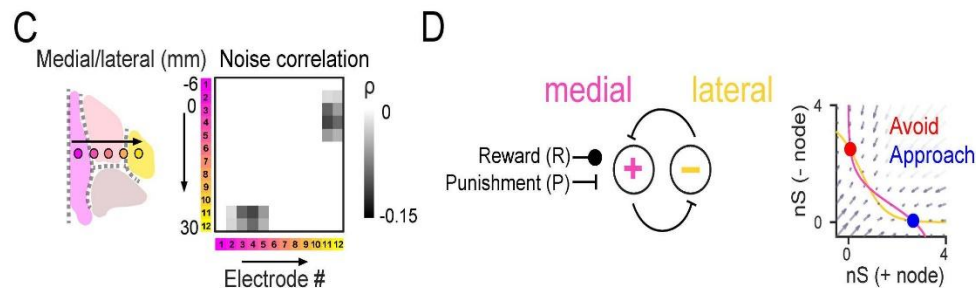


Results

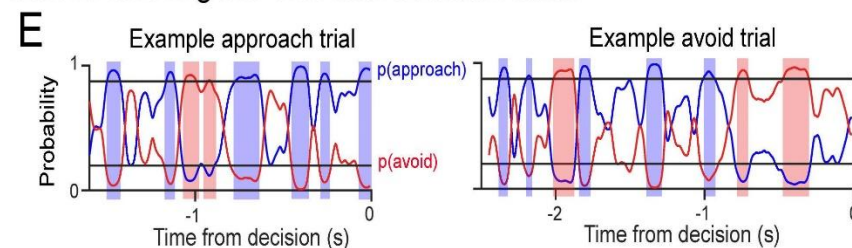
OFC contains two Clusters of responses that are anatomically separate:



OFC responses are anticorrelated across the medial-lateral axis, invoking a two-node mutual inhibition circuit:



OFC dynamics on single trials alternate between approach and avoidance, before favoring the eventual decision state:



Disclosures: C.K. Starkweather: None. E.H. Willbrand: None. K.K. Sellers: None. P. Hullett: None. A. Krystal: None. K.S. Weiner: None. J.T. Willie: None. P. Brunner: None. M. Hsu: None. E.F. Chang: None. R.T. Knight: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.10/DD8

Topic: I.04. Executive Functions

Title: Hierarchical Prefrontal Contributions to Perceptual Decision-making

Authors: *X. SHEN¹, I. PAPPAS², R. KEERATIVITTAYAYUT³, C. PAMARAPA⁴, C. CHUNHARAS⁵, S. ITTHIPURIPAT⁶, I. C. BALLARD⁷;

¹Psychology, Univ. of California, Riverside, Riverside, CA; ²USC's Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA; ³Sch. of Radiological Technology, Fac. of Hlth. Sci. Technol., ⁴Chulabhorn Royal Acad., Bangkok, Thailand; ⁵Neurology, department of Intrnl. Med., KCMH, Chulalongkorn Univ., Bangkok, Thailand; ⁶Neurosci. Ctr. for Res. and Innovation, Learning Inst., KMUTT, Bangkok, Thailand; ⁷Helen Wills Neurosci. Inst., UC Riverside, Riverside, CA

Abstract: In visual decision-making, both high-level semantic information and low-level visual properties influence choice, for example, when selecting a pastry based on both its type and appearance. However, the strong correlation between these low and high-level features in natural stimuli makes their individual contributions challenging to isolate. To address this, we used a deep neural network to generate a stimulus set in which high- and low-level visual similarities were decorrelated. In the task, 20 male and female participants judged the similarity between a root image and two alternatives (Image1 and Image2), differing in their low- and high-level similarities to the root image. Behaviorally, participants were highly sensitive to high-level similarity, but also showed an additive effect of low-level similarity. When high- and low-level features aligned, participants were ~20% more likely to choose the image compared to trials where the features conflicted. Neuroimaging results showed that activation in the middle frontal gyrus (MFG) increased with both high- and low-level visual similarity. Strikingly, we observed an anterior-posterior gradient within the MFG, with anterior regions linked to higher-level similarity and posterior regions to lower-level similarity. At choice, we also found that high-level visual information has a stronger representation in ventral PFC regions, whereas dorsal regions exhibit stronger coding for low-level visual information. Together, these findings suggest that the prefrontal cortex integrates high- and low-level visual information in a hierarchically organized manner, mirroring the structure of the visual stream, to guide perceptual decisions.

Disclosures: X. Shen: None. I. Pappas: None. R. Keerativittayayut: None. C. Pamarapa: None. C. Chunharas: None. S. Itthipuripat: None. I.C. Ballard: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.11/DD9

Topic: I.04. Executive Functions

Support: NIH grant R01MH132386
NIH grant R01MH112746
NIH grant 1U01MH121766
NIH grant DP5OD012109-01

Title: Contingency representations in prefrontal cortex unify goal-directed planning and working memory

Authors: *J. MILLER^{1,2}, E. CHO³, D. EHRLICH⁴, N. P. SANTAMAURO², Y. CHO², J. D. MURRAY^{2,3};

¹Univ. of Miami, Coral Gables, FL; ²Dept. of Psychiatry, Yale Univ., New Haven, CT;

³Dartmouth Col., Hanover, NH; ⁴Univ. of California, Berkeley, Berkeley, CA

Abstract: Working memory (WM) is critical in guiding our adaptive behavior based on immediate and future demands, and the prefrontal cortex (PFC) and a network of connected areas are consistently active during WM. But, it remains difficult to parse out the differential contributions of brain areas to WM function, especially when maintenance and usage of WM content is often intertwined. How do representations for stimuli, task rules, and future behavior all contribute to WM, and what is their brain circuit organization? A recently developed computational framework and task paradigm helps unify the representational geometry for goal-directed planning and WM (Ehrlich & Murray, 2022). In this conditional delayed logic (CDL) task, patterns of human behavior and activity in neural networks suggest combined representations of stimuli and task rules into response contingencies. We tested for differential neural substrates of stimulus, rule, and newly predicted contingency representations using a version of the CDL task adapted for functional MRI.

On each trial, human participants were shown a rule cue (colored box), gabor stimulus (vertical/horizontal), followed by a jittered delay period, and then a second gabor (vertical/horizontal), after which they responded with a left or right hand button press. The correct response on each trial was determined based on a combination of the previously learned rule, and the orientation of the first and second stimuli. During the WM delay, voxel activity patterns across frontal cortex differentiated among contingency states. Maps of contingency representations often overlapped with rule representations, however, contingency sensitive voxels were specific to anterior PFC areas.

To better understand areal differences in task representations, we constructed neurobiologically-informed, multi-area recurrent neural networks trained on a version of the CDL task. This multi-area model developed a functional hierarchy: a sensory module that persistently maintains the identity of the first sensory cue, an associative module encoding flexible upcoming responses based on a future cue, and a pre-motor module predominantly maintaining specific outputs until the end of a delay. Patterns of contingency encoding learned by the network showed representational alignment for task coding across human association cortex, and these representations were strongly supported by recurrent connectivity in the network. In sum,

prefrontal areas in the human brain displayed unique representations of task contingencies and subserve WM by integrating different task information to plan future behavior.

Disclosures: J. Miller: None. E. Cho: None. D. Ehrlich: None. N.P. Santamauro: None. Y. Cho: None. J.D. Murray: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.12/DD10

Topic: I.04. Executive Functions

Support: NIH Grant R01MH121509

Title: Dissociable causal contributions of the dorsolateral prefrontal cortex and lateral frontal pole to the stability and flexibility of cognitive control

Authors: J. LEE¹, A. MEYER², K. GLADHILL³, A. DORFMAN², S. GOULD², *D. E. NEE²; ²Dept. of Psychology, ³Dept. of Behavioral Sci. and Social Med., ¹Florida State Univ., Tallahassee, FL

Abstract: Cognitive control supports intentional, goal-directed behaviors when habits will not suffice. Context-appropriate behavior requires a balance between stably maintaining task sets in the face of interference, and flexibly adjusting task sets in response to environmental changes. The lateral prefrontal cortex (LPFC) is central to cognitive control, consisting of several neocortical areas that perform distinct functions. How the coordinated action of distinct LPFC areas contributes to the stability and flexibility necessary for cognitive control remains elusive. Here, we used intermittent theta-burst transcranial magnetic stimulation (iTBS) to causally contrast the roles of the dorsolateral prefrontal cortex (DLPFC) and lateral frontal pole (FPI) in humans. Both areas were identified by the same personalized fMRI activation contrast and stimulation to each area was matched using e-field modeling. In separate counterbalanced visits, cognitive control performance and fMRI activations were assessed following iTBS to each LPFC site, as well as following iTBS to a control site (S1), and no-iTBS. Behavioral measures of stability (mixing costs) and flexibility (switch costs) both tended to improve following DLPFC-iTBS but worsen following FPI-iTBS. Concomitantly, control-related activations diminished following DLPFC-iTBS, but increased following FPI-iTBS. These data are inconsistent with a push-pull/tradeoff between stability and flexibility. Instead, the DLPFC and FPI each appear to support both stability and flexibility, but do so in opposite ways from one another. DLPFC-iTBS/FPI-iTBS may sharpen/de-tune control representations jointly affecting both stability and flexibility.

Disclosures: J. Lee: None. A. Meyer: None. K. Gladhill: None. A. Dorfman: None. S. Gould: None. D.E. Nee: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.13/DD11

Topic: I.04. Executive Functions

Title: Mapping the mesoscale human cortical connectome

Authors: *R. XU¹, A. TAKAHASHI¹, A. BUSH², N. SISTERSON², A. WALTON^{2,1}, S. HUTCHINSON¹, C. NEUDORFER², A. KAMMEN², V. KOKKINOS², N. JHINGAN¹, A. FUNG¹, A. MARVI¹, C. J. VALENZUELA¹, H. KEAN¹, R. PRAMOD¹, E. G. MCMAHON¹, S. YEE³, J. KIRSCH^{4,3}, N. G. KANWISHER¹, E. FEDORENKO¹, R. DESIMONE¹, M. RICHARDSON²;

¹MIT, Cambridge, MA; ²Neurosurg., ³Radiology, Massachusetts Gen. Hosp., Boston, MA;

⁴Athinoula A Martinos Ctr. for Biomed. Imaging, Charlestown, MA

Abstract: Dozens of regions of the human cerebral cortex have been identified that have distinctive, often highly selective responses. These regions are present in approximately the same location in virtually all neurotypical adults. Yet we do not know with any certainty how these cortical regions are structurally connected to each other or to the rest of the brain. In macaques, we have utilized concurrent electrical stimulation and fMRI (es-fMRI) to map fine-grained connectivity, and the results are highly consistent with the “ground truth” tracing data. We now translate this approach to identify the projections of functionally specific cortical regions in human epilepsy patients with clinically implanted intracranial electrodes, combined with task fMRI to identify regions engaged in language, social cognition, object vision, etc. We made converging findings across 41 frontotemporal stimulation sites in eight individuals. First, we found that anatomically connected cortical sites are much more likely to share functions than unconnected sites, consistent with the idea of a network of related regions. Second, the connections of a given site tended to span only a subset of any functional network in which the site is located, and they varied systematically with the site’s location, suggesting the existence of subnetworks that may be difficult or impossible to detect using other fMRI methods. Third, while previous fMRI studies have emphasized the dissociations of specialized networks, our approach also begins to uncover a non-trivial portion of connections across networks. They include both hierarchical connections, i.e., between a high-level network and its sensory input, such as between the fusiform face area and retinotopic visual areas, and “lateral” connections that involve similar-level networks, such as language and social cognition, and face and object processing. Fourth, the ratio of within- vs. cross-network connections didn’t vary much with distance, even though cortical sites further apart generally had less shared functions, suggesting long-range connectivity is especially functionally specific. Finally, we found a moderate yet inherent correspondence between es-fMRI and resting-state functional connectivity, which was NOT a byproduct of their shared dependence on functional similarity and physical proximity. These findings put tangible constraints on the development of mechanistic models of human cognition.

Disclosures: R. Xu: None. A. Takahashi: None. A. Bush: None. N. Sisterson: None. A. Walton: None. S. Hutchinson: None. C. Neudorfer: None. A. Kammen: None. V. Kokkinos: None. N. Jhingan: None. A. Fung: None. A. Marvi: None. C.J. Valenzuela: None. H. Kean: None. R. Pramod: None. E.G. McMahon: None. S. Yee: None. J. Kirsch: None. N.G. Kanwisher: None. E. Fedorenko: None. R. Desimone: None. M. Richardson: None.

Poster

PSTR041: Influence of Prefrontal Cortex Organization on Cognition

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR041.14/DD12

Topic: I.04. Executive Functions

Support: NSF Grant 2419387
University of Tampa Professional Development Award

Title: Humans remove negative-value but not low-value verbal memoranda from working memory even during rehearsal disruption

Authors: *S. FESTINI, M. MENDEZ, C. MEYER, B. TORRES, A. SCHULTZ, T. WILSON, R. AGUILAR;
Univ. of Tampa, Tampa, FL

Abstract: Proactive interference (PI) occurs when previously learned information disrupts current performance. Prior research within working memory (WM) indicates that participants exhibit longer response times and reduced accuracy when probed with recent memoranda that originated from the prior WM trial as opposed to the current trial. Thus, assessments of the magnitude of PI can provide a window into the persisting strength of memory representations, as stronger memories will yield more interference. Directed forgetting instructions have been shown to reduce PI within WM in humans. Yet, value-directed remembering manipulations within WM can have disparate effects, depending on whether negative- or low-value cues are provided. The current study evaluated whether rehearsal-disrupting articulatory suppression impacted prioritization in WM as a function of value-cue type (negative-value or low-value). Healthy human younger adults performed an item-recognition WM task (60 trials) with a recent probes manipulation to induce PI. Memoranda were assigned either negative (-5) vs. positive (5) point values ($n = 64$) or low (1) vs. high (10) point values ($n = 65$) after encoding. Occasionally, PI was induced by probing a recent item from the prior WM trial as opposed to the current trial. Participants were required to perform articulatory suppression by repeating the word “the” continuously during the value-cue presentation (2 s) and retention interval (3 s). Importantly, a different pattern of results emerged for negative- compared to low-value cues. With negative-value cues, participants exhibited less PI for negative-value information, even with the required articulatory suppression. Specifically, accuracy was significantly better for negative-cued recent probes than positive-cued recent probes, and, when responding correctly, response times were significantly shortened for recent-negative relative to recent-positive items. In contrast, when

low-value cues were provided, participants exhibited similar PI for both low- and high-value memoranda, evidenced in both accuracy and response times. These data inform theories of prefrontal mechanisms overseeing the executive control of WM, indicating that, even when executive demands and articulatory rehearsal are taxed, if individuals know that certain information is harmful to maintain, they better remove those detrimental representations from WM and experience less PI, similar to following directed forgetting instructions. Nevertheless, if certain information is designated as less important, but still relevant, humans tend to maintain this information in mind, allowing PI to persist in WM.

Disclosures: S. Festini: None. M. Mendez: None. C. Meyer: None. B. Torres: None. A. Schultz: None. T. Wilson: None. R. Aguilar: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.01/Web Only

Topic: I.05. Working Memory

Support: SECIHTI Grant CBF2023-2024-1641

Title: Sex-based differences in cognitive and metabolic impact of high-fat/carbohydrate-rich diet and diabetes in mice

Authors: *S. J. LOPEZ-PEREZ¹, A. LOMELI LEPE², M. E. URENA-GUERRERO³;

¹CUCBA-Universidad de Guadalajara, Zapopan, Jalisco, Mexico; ²Univ. de Guadalajara, Univ. de Guadalajara, Zapopan, Mexico; ³Biología Celular y Mol., Univ. de Guadalajara, CUCBA., Zapopan, Guadalajara, Mexico

Abstract: There exists a well-documented association between diabetes and cognitive decline, which has further been implicated in the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease. Dietary habits play a critical role in the onset of diabetes, and the correlation between this metabolic condition and cognitive impairment, with consideration of sex as a biological variable, needs further investigation. The objective of the present study was to examine these relationships and explore the differential effects based on sex. Male and female CD-1 mice, with an initial weight of 35-40 g, were subjected to a high-fat and carbohydrate-rich diet (HF-CRD) over a period of four weeks. Following this dietary regimen, the mice received two intraperitoneal doses of the diabetogenic agent alloxan (150 mg/kg), administered with an interval of one day between treatments. Seventy-two hours post-administration, subjects with blood glucose levels exceeding 200 mg/dL were selected for further study. The mice were subsequently allowed to develop diabetic condition over a five-week period, after which behavioral assessments were conducted using the Barnes maze and the novel object recognition test—two methodologies widely employed to measure spatial memory and non-procedural short-term memory. The findings revealed significant sex-based differences in the metabolic

parameters of the animal model. Males subjected to the HF-CRD exhibited a more rapid weight gain compared to females ($\Delta 6.07 \pm 1.90$ in males versus 2.87 ± 2.02 in females after 8 weeks of diet). Following the induction of diabetes, females tended to lose weight, whereas males continued to gain weight. Regarding blood glucose levels, males displayed an increase after eight weeks of dieting (195.3 ± 15.36 mg/dL), while females showed stability in their levels (133 ± 15.44 mg/dL). Moreover, 72 hours post-diabetes induction, blood glucose concentrations were higher in males (254.3 ± 23.87 mg/dL) compared to females (218.71 ± 25.85 mg/dL). Behavioral outcomes also demonstrated sex-specific differences. Male mice performed more effectively in the Barnes maze, as evidenced by shorter latencies in locating the maze's exit. Conversely, female mice exhibited superior performance in the novel object recognition test, indicating a stronger ability to recall previously explored objects. These results highlight sex-related differences in weight gain management and hyperglycemia, as well as spatial and recognition memory abilities; the latter suggests distinct brain mechanisms in the context of dietary habits related to diabetes.

Disclosures: S.J. Lopez-Perez: None. A. Lomeli Lepe: None. M.E. Urena-Guerrero: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.02/DD13

Topic: I.05. Working Memory

Title: Sex-specific effects of ENT2 deletion on cognitive and behavioral phenotypes in aging Tau22 mice

Authors: *P.-C. KUO, C.-J. LIN;
Sch. of Pharm., Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Introduction: Tauopathy contributes to progressive cognitive and behavioral impairments in Alzheimer's disease, often exacerbated by aging. The Tau22 transgenic mouse model, which bears mutant human tau, displays age-related deficits in memory, emotional regulation, and goal-directed behavior. Equilibrative nucleoside transporter 2 (ENT2), a key regulator of brain metabolism and neuronal activity, has been implicated in neuronal adaptation to metabolic stress. Given known sex differences in both tauopathy progression and neurometabolic regulation, ENT2 may differentially influence tau-related phenotypes across sexes; however, its behavioral relevance remains unclear. **Objective:** To examine the impact of ENT2 deletion on recognition memory, anxiety-like behavior, and goal-directed performance in aging male and female Tau22 mice. **Methods:** Twelve-month-old male and female Tau22 and Tau22-ENT2 knockout (KO) mice were evaluated using the Novel Object Recognition Test (NORT), Elevated Plus Maze (EPM), and Nesting Test. Wild-type (WT) and ENT2 KO littermates were used as controls. **Results:** In NORT, male Tau22-ENT2 KO mice showed significantly improved recognition memory compared to Tau22, suggesting a protective effect of

ENT2 deletion; no improvement was observed in females. In the EPM, Tau22 mice—regardless of sex—spent more time in the open arms than WT, indicating either reduced anxiety or impaired environmental risk assessment. ENT2 deletion did not alter this behavioral phenotype. In the Nesting Test, female Tau22 mice showed significantly impaired goal-directed behavior compared to WT, while Tau22 males exhibited a downward trend that did not reach significance. ENT2 deletion had no apparent effect on nesting behavior in either sex. **Conclusion:** In the context of aging, ENT2 deletion selectively improves recognition memory in male Tau22 mice but has no impact on anxiety-like behavior and nesting function. Behavioral impairments were more pronounced in females. These findings highlight the sex-dependent roles of ENT2 in modulating tauopathy-related phenotypes and underscore the importance of considering sex as a biological variable in therapeutic strategies.

Disclosures: P. Kuo: None. C. Lin: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.03/DD14

Topic: I.05. Working Memory

Support: Ann S. Bowers Women's Brain Health Initiative (EGJ)
Alfred P. Sloan Research Fellowship (TCS)
UCSB Faculty Research Assistant Program
UCSB Undergraduate Research & Creative Activities Grant

Title: Relationship between pupil size and visual working memory performance is stable across sex hormone fluctuations throughout the menstrual cycle

Authors: *R. SINHA¹, Y. LI², E. MURATA³, H. GROTZINGER⁴, E. G. JACOBS⁵, T. C. SPRAGUE⁶;

¹Univ. of California, Santa Barbara, Goleta, CA; ²Psychological & Brain Sci., ³Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; ⁴Psychological and Brain Sci., Univ. of California, Santa Barbara, SANTA BARBARA, CA; ⁵UC Santa Barbara, Santa Barbara, CA; ⁶Psychological and Brain Sci., UC Santa Barbara, Goleta, CA

Abstract: Working memory (WM) refers to the cognitive system responsible for the temporary storage and manipulation of information necessary for decision-making and adaptive behavior (Baddeley, 2010; Ma et al., 2014). There is evidence that fluctuations in sex hormones modulate prefrontal-dependent processes such as selective attention and cognitive control which are critical for WM (Jacobs and D'Esposito, 2011). However, it remains unclear how everyday fluctuations impact WM performance. Previous studies (Robison and Unsworth, 2019; Starc et al., 2017) have shown larger change in pupil size from baseline during encoding or the WM delay period is linked to better WM performance. As hormonal changes may lead some

participants into a state of hyperarousal and push others beyond the optimal arousal range, individual differences in the relationship between arousal (pupil size change) and WM error may emerge. As such, comparing changes in pupil size to WM recall error may provide a trial by trial assay of the impacts of hormones on WM behavior. Here, we investigated the relationship between sex hormone (i.e., estradiol, progesterone, cortisol, testosterone) levels and WM performance by analyzing the relationship between pupil size changes and WM recall error across both sexes. In our study, we densely sampled 10 naturally cycling female participants who completed a Change Localization Task (Zhao et al., 2023) and a Memory-Guided Saccade (MGS) task (Funahashi et al., 1989; Li and Sprague, 2023) every other day over a menstrual cycle and 10 male participants. We quantified changes in pupil size during encoding and delay periods of the MGS task to assess the coupling between pupil-based measures of arousal and WM performance. Mixed effect modeling using menstrual cycle phase (i.e., early follicular phase, ovulatory phase and mid luteal phase), WM capacity, and pupil size change during encoding and delay from female participants revealed a main effect of cycle phase and a main effect of pupil size change during encoding, indicating pupil dilation during encoding is associated with greater memory error. Additionally, there was a significant interaction between menstrual cycle phase and pupil size change during delay, such that greater delay period pupil dilation predicted smaller WM error during the ovulatory phase only. This suggests that coupling between pupil dynamics and WM recall error is not static across the menstrual cycle, underscoring the importance of hormone state in mediating cognitive behaviors.

Disclosures: R. Sinha: None. Y. Li: None. E. Murata: None. H. Grotzinger: None. E.G. Jacobs: None. T.C. Sprague: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.04/DD15

Topic: I.05. Working Memory

Support: R01EY02Institutes5999

Title: Age-related impairments in auditory working memory for tones are driven by a selective impairment in familiarity, not recollection.

Authors: *C. HAWKINS, A. P. YONELINAS;
Univ. of California, Davis, Davis, CA

Abstract: Prior work has suggested that visual working memory as measured in change detection tasks can be based on recollection, whereby participants consciously identify a specific feature of a stimulus that has changed, or on assessments of familiarity, whereby participants sense that a change has occurred but are unable to consciously identify what has changed. Recent work revealed that the two processes also support auditory working memory (aWM)

performance in younger adults, and that they are functionally dissociable in a manner analogous to visual working memory. Whether recollection and familiarity support auditory working memory in older adults, and whether they dissociate in aging, remains unclear. The present change detection study sought to address that gap in knowledge by having older adults make confidence judgments about whether pairs of speech sounds and pure tones presented through headphones were the same or different. Overall performance between younger and older adults was comparable for speech sounds, but an examination of parameter estimates revealed that older adults showed reduced familiarity for all conditions compared with younger adults. However, for pure tones, overall performance for older adults was lower than for younger adults. Critically, this performance difference was driven entirely by a selective reduction in estimates of familiarity in older adults compared with younger. Moreover, when overall performance was matched between age groups, older adults still showed a significant, selective reduction in estimates of familiarity compared with younger adults. The results indicate that recollection and familiarity contribute to aWM for speech sounds and pure tones in older adults, and that the processes may be differentially impacted in aging.

Disclosures: C. Hawkins: None. A.P. Yonelinas: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.05/DD16

Topic: I.05. Working Memory

Support: NIH Grant R01AG047972
NIH Grant R01AG029523
NIH Grant R01NS106711
NIH Grant R01NS106702

Title: Cognitive speed and neural predictors of age-related changes in working memory

Authors: *E. J. SMITH¹, Y. ZHAO², G. SHERARD¹, M. ANDREO¹, D. H. ABDELKARIM³, B. RYPMA¹;

¹Univ. of Texas at Dallas, Richardson, TX; ²Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA; ³Univ. of Illinois, Urbana-Champaign, IL

Abstract: Working memory (WM) is comprised of distinct processing components (i.e., encoding, maintenance, and retrieval). Age-related declines in processing speed and volumetric brain changes are known to underlie age-related WM decline; however, there is a gap in understanding the specific speed-related and neural mechanisms involved in WM component changes with age. We hypothesized that age-related changes in distinct WM components might be affected by changes in distinct cognitive speed abilities (i.e., motor, perceptual, and processing speed) and distinct neural mechanisms. To explore this hypothesis, we examined

neuropsychological and structural MRI data in healthy human participants ($n = 94$; 46 older adults (OA), 48 younger adults (YA)). During scanning, participants completed a parametric Sternberg Working Memory (SWM) task, in which they were shown six letters in each trial, with either 2, 4, or 6 of the letters surrounded by brackets (indicating the to-be-remembered letters). Following a 4000 ms delay interval, a single letter appeared, and participants decided whether that letter was or was not in the previous brackets. Reaction times (RT) were collected across set sizes. Intercepts (indexing WM encoding and motor response) and slopes (indexing WM maintenance and retrieval) for each participant's SWM RT function were calculated. Participants also completed a T1 structural MRI, and a series of neuropsychological tests measuring motor, perceptual, and processing speeds. We observed strongly significant negative correlations between SWM intercept and motor speed ($r = -0.44, p = .002$), and perceptual speed ($r = -0.36, p = .02$) in OAs, but not YAs (motor speed: $r = -0.13, p = .39$; perceptual speed: $r = -0.28, p = .0503$). There were significant negative correlations between SWM intercept and left precentral gyrus volume (involved in motor function; $r = -0.30, p = .04$), and left lateral occipital cortex volume (involved in visual perception; $r = -0.35, p = .02$) in OAs, but not YAs (left precentral: $r = -0.25, p = .09$; left lateral occipital: $r = -0.21, p = .15$). These results suggest that faster perceptual and motor speeds were associated with faster WM encoding and motor response in OAs. Furthermore, they suggest that age-related atrophy in corresponding motor and visual regions is associated specifically with slower encoding and WM motor response. Together, these results begin to illuminate specific mechanisms underlying WM changes in aging. We will continue to assess relationships between specific SWM components and the extent to which age differences in neurophysiological metrics might control for variability in the distinct cognitive speed abilities.

Disclosures: E.J. Smith: None. Y. Zhao: None. G. Sherard: None. M. Andreo: None. D.H. Abdelkarim: None. B. Rypma: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.06/EE1

Topic: I.05. Working Memory

Support: R01AG074808

Title: Ecoviv does not adversely impact working memory performance of aged mice

Authors: *E. B. HOANG, M. NOBACK, J. A. FIELDS, B. L. HENRY, R. J. ELLIS, J. W. YOUNG;
Psychiatry, Univ. of California San Diego, La Jolla, CA

Abstract: Background: Despite combined antiretroviral therapy's (cART) effectiveness, many people with HIV (PWH) continue to experience cognitive impairment, persisting with viral

suppression and may be influenced by aging, which contributes to brain function and cognitive changes. Animal models such as ecoHIV in aged mice can help investigate cognitive domains affected by chronic HIV-like infection in an aging population. Prior studies conducted in older animals have reported mixed findings regarding ecoHIV's impact on memory and learning. We used aged C57BL/6J mice, evaluating whether ecoHIV infection impairs working memory (WM), sucrose preference, or habituation in the open field, aiming to identify domain-specific effects to inform future therapeutics for a HIV-Associated Neurocognitive Disorders (HAND) in aging populations. **Methods:** We used 16-19-month-old C57BL/6J mice (n=32; 17 females and 15 males) and trained them on the Radial Arm Maze until their performance on the task remained consistent. Animals were then counterbalanced into groups for Radial Arm Maze (RAM) based on working memory performance (n=32) then infected with sham solution (1x Phosphate Buffered Saline) or ecoHIV virus. A subset of the animals (n = 19; 10 females and 9 males) were further tested on sucrose preference test (SPT) and open field tests (OFT) of habituation. We hypothesized ecoHIV-infected animals would perform worse on the RAM, show decreased sucrose preference, and habituate less in the OFT. **Results:** No significant ecoHIV effects were observed for the RAM, measured by the WM span ($\eta^2 = 0.057$, $p=0.205$), WM errors ($\eta^2 = 0.028$, $p=0.377$) reference errors ($\eta^2 = 0.000$, $p=0.931$) or sucrose preference ($\eta^2 = 0.0056$, $p=0.806$). EcoHIV-infected mice habituated more in the OFT ($\eta^2 = 0.285$, $p=0.027$) which was calculated using a two-way ANOVA. No sex or sex interactions were observed for measures of the RAM, sucrose preference or habituation tasks.

Conclusions: Our findings indicate that ecoHIV did not adversely affect working memory in the RAM or sucrose preference in the aged mice, implying that ecoHIV may not affect aspects of working memory. Unexpectedly, we observed enhanced habituation, a form of learning, the in ecoHIV-infected aged mice. It is possible that age and ecoHIV may interact and affect other cognitive domains, which remain to be tested.

Disclosures: E.B. Hoang: None. M. Noback: None. J.A. Fields: None. B.L. Henry: None. R.J. Ellis: None. J.W. Young: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.07/Web Only

Topic: I.05. Working Memory

Support: PAPIIT-UNAM IN217221 to AERC

Title: Difference in working memory in young and old adults: Trait and State anxiety/depression as a predicted factor

Authors: *I. GÓMEZ GONZÁLEZ¹, E. LÓPEZ-GONZÁLEZ², A. E. RUIZ-CONTRERAS³, U. CABALLERO SANCHEZ⁴, O. PROSPERO-GARCIA⁵, O. PROSPERO-GARCIA⁶;

¹Univ. Nacional Autónoma de México, CDMX, Mexico; ²LNGC, Univ. Nacional Autonom de

Mexico, Mexico City, Mexico; ³Lab. Neurogenomica Cognitiva, Fac. Psicología, Univ. Nacional Autonoma de Mexico, D.F., Mexico; ⁴Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; ⁵UNAM, Mexico city, Mexico; ⁶Inst. De Neurobiología, UNAM, CDMX.

Abstract: Working memory (WM) enables the temporary storage and manipulation of information necessary for performing goal-directed tasks. Previous research has shown that WM efficiency can be affected by age and emotional states, particularly anxiety and depression. Additionally, valence stimuli impact performance in WM, and this effect may vary depending on the individual's age. Specifically, high levels of anxiety and depression have been associated with increased susceptibility to interference from emotional content. The aim was to examine whether the relationship between anxiety and depression levels and WM efficiency for emotional stimuli differs between young and older adults. Thirty-nine young adults (aged 20-29) and twenty-eight older adults (aged 60 and above) participated. All participants were right-handed and reported no history of neurological or psychiatric conditions, nor severe substance dependence. Measures of trait and state anxiety and depression were administered, along with a WM task in which participants had to recognize emotionally valence faces (positive, negative, or neutral) previously presented during the encoding phase alongside a visual distractor. Findings revealed that higher levels of trait anxiety, trait depression, and state depression were significantly associated with lower WM efficiency in young adults, but not in older adults. Furthermore, among younger participants, negatively valence stimuli predicted reduced WM performance as scores on trait anxiety and depression increased. These results highlight potential age-related differences in the emotional modulation of working memory and its interaction with affective symptomatology.

Disclosures: I. Gómez González: None. E. López-González: None. A.E. Ruiz-Contreras: None. U. Caballero Sanchez: None. O. Prospero-Garcia: None. O. Prospero-Garcia: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.08/EE2

Topic: I.05. Working Memory

Title: Working Memory and Orthographic Processing as Predictors of Reading Comprehension in Mexican University Students

Authors: *D. BOLANOS-RAMIREZ, E. VILLUENDAS-GONZALEZ;
Psychology, Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico

Abstract: Working memory plays a vital role in reading comprehension by enabling the integration and manipulation of information. Reading comprehension relies on several cognitive functions, including language skills, memory and attention. It involves not only decoding written text but also drawing on prior knowledge and overall reading proficiency. Working memory is

essential for language comprehension, learning, and reasoning, helping individuals form internal representations that guide decision-making and behavior. Numerous studies have emphasized the importance of strong reading abilities for academic success at all educational levels, particularly at the university level, where reading comprehension is essential for sustained academic performance throughout the academic year. **AIM:** This study aimed to examine the relationship between working memory, orthographic knowledge, and reading comprehension among Mexican university students. **METHODS:** The researchers utilized and improved electronic version of the Sternberg task, adapted to include memory loads of five elements, to assess working memory. In addition, they employed a reading comprehension test and the Adult Spelling Knowledge Battery -specifically the error detection in a text subtest- to evaluate reading skills. Twenty-two first-year undergraduate students (17 females, 5 males) from a Mexican university participated in the study. **RESULTS:** Results from a multiple regression analysis using backward elimination method showed two significant models predicting reading comprehension in a sample of 22 participants. Model 1 included working memory and orthographic knowledge (dictation task) as predictors, $F(2,19)=3.60$, $p=.047$, adjusted $R=.198$, $RMSE=3.93$. In this model, only orthographic knowledge (dictation) was significant predictor ($b=-0.438$, $p=.044$). Model 2 retained only this predictor, yielding a better fit, $F(1,20)=6.34$, $p=.020$, adjusted $R=.203$, $RMSE= 3.92$, with a standardized coefficient of $B=-0.491$ ($p=.020$). These findings suggest that orthographic knowledge, as measured by a dictation task, plays a relevant role in reading comprehension. Further research is needed to clarify the direction and nature of this relationship.

Disclosures: D. Bolanos-Ramirez: None. E. Villuendas-Gonzalez: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.09/EE3

Topic: I.05. Working Memory

Support: Convocatoria Becas Nacionales para estudios de Posgrado 2024-2:
4036648

Title: Design of technology for mild cognitive impairment screening: adaptation of associative tasks to digital phenotyping

Authors: *H. ZAPATA ROBLES¹, R. LOERA-VALENCIA², R. CORNEJO¹;

¹Univ. Autónoma de Chihuahua, Chihuahua, Mexico; ²Karolinska Inst., Chihuahua, Mexico

Abstract: This project proposes the design of an innovative technology for the screening of Mild Cognitive Impairment (MCI), a critical preclinical stage of Alzheimer's disease, with a particular focus on the Mexican population. The motivation stems from the increasing global and national prevalence of Alzheimer's, with projections estimating 3.5 million cases in Mexico by 2050, the lack of large and representative datasets for machine learning algorithms, and the scarcity of

specialized health care to detect cognitive decline. This scarcity limits the "tropicalization" of predictive models. Additionally, Mexico faces a significant technological gap affecting older adults, the population most vulnerable to Alzheimer's disease. To address these challenges, we propose a solution focusing on digital phenotyping, i.e., the real-time collection of behavioral and cognitive data through mobile devices. In this context, associative tasks from the Reinforcement Learning Working Memory (RLWM) model were adapted. These tasks have proven effective in analyzing the influence of working memory on decision-making and in distinguishing between individuals with and without cognitive impairment, showing sensitivity to aging-related decline. The design methodology for the technology follows a user-centered, iterative approach (UCD), including focus group sessions with older adults to identify their needs, motivations, and technological preferences. Collaboration with experts in Human-Computer Interaction (HCI), computational psychiatry, gerontology, and neuroscience will also be integral. We present a low-fidelity prototype, and its evaluation of usability and functionality compared to the MoCA test. The overarching goal is to create a national database on cognitive impairment in the Mexican population, enabling the development of more accurate and representative predictive models. This effort aims to lay the technological groundwork for future research on the relationships between working memory, decision-making, and genetic factors in the prevalence of MCI, while also improving technological accessibility for older adults.

Disclosures: H. Zapata Robles: None. R. Loera-valencia: None. R. Cornejo: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.10/EE4

Topic: I.05. Working Memory

Support: Korea Basic Science Institute (National research Facilities and Equipment Center) grant funded by the Ministry of Education (RS-2024- 00435727) National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (RS-2024-00349515, RS-2023-00276729)

Title: When the Future Shapes the Past: Retrospective Modulation of Visual Working Memory by Estimation Timing and Saliency Relative to Subsequent Input

Authors: *M. CHOE, S.-H. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Visual working memory engages dynamic representations that are constrained by limited neural resources [1, 2]. While these dynamics have typically been characterized using items presented simultaneously, we designed a series of experiments using sequentially presented items to examine how the memory of an item encoded earlier is affected by the resources allocated to items encoded subsequently. Human participants performed delayed

orientation estimation tasks, where they viewed two stimuli shown sequentially and then reproduced the orientation of the post-cued stimulus from memory. The orientations of both stimuli were independently drawn from a uniform distribution spanning 180 degrees, and the stimuli appeared at a random location among eight possible positions arranged on a circle with a radius of 3 degrees of visual angle. We found that the orientation memory of the first stimulus was repelled by the second stimulus. This phenomenon, termed ‘retrospective repulsion bias,’ was most pronounced when the first stimulus was estimated immediately after the second stimulus, and it decreased as the estimation timing was delayed. The retrospective repulsion bias was also influenced by the saliency of the second (uncued) stimulus compared to the first (cued) stimulus: as the second stimulus became less salient, the bias shifted from repulsion to attraction. These findings indicate that the memory states of past targets undergo temporary modifications due to the encoding of following targets, with the degree of this modification being influenced by the relative saliency of the later targets. To explain retrospective repulsion bias and its modulation by estimation timing and relative saliency, we propose that the cognitive act of encoding new items into feature memory space depletes representational resources and reallocates them toward the newly encoded feature. We further posit that this resource reallocation creates a gradient of coding efficiency, which pushes the memory states of earlier items away from the newly encoded feature, with the degree of this repulsive push determined by the resources allocated to the subsequent items. To validate the ‘resource gradient’ hypothesis, we developed an attractor-network model based on its key assumptions, demonstrating that dynamic working memory representations explain the observed biases in human delayed estimation performance. **Reference** [1] Gu, H. et al., (2023). Decision-consistent bias mediated by drift dynamics of human visual working memory. *bioRxiv*, 2023-06. [2] Tomić, I., & Bays, P. M. (2024). A dynamic neural resource model bridges sensory and working memory. *Elife*, 12, RP91034.

Disclosures: M. Choe: None. S. Lee: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.11/EE5

Topic: I.05. Working Memory

Support: NIH; NIDA Grant: DA058909

Title: Modeling symbolic processes in rodents: the formation of equivalence classes through a reversal learning paradigm

Authors: *A. C. WILLIAMS¹, K. G. QUANN², K. E. BRUCE¹, J. GALIZIO²;

¹Psychology, Univ. of North Carolina Wilmington, Wilmington, NC; ²Psychology, Univ. of North Carolina Wilmington, WILMINGTON, NC

Abstract: Symbolic processes play a fundamental role in human behavior, but modeling these processes using nonhumans has been a challenge. One property of symbolic learning that has been found in animals is the formation of equivalence classes in which stimuli become functionally interchangeable. Such classes have been found in sea lions, but a rodent model would be of more use to study the neurobiology of symbolic processes. Using a successive discrimination procedure, 12 male Sprague Dawley rats (90 days of age at the start of testing) were trained to form classes using odor stimuli. Classes were organized by assigning four odors to each class, for a total of eight stimuli. Responses to four of the odors in the positive set (S+) resulted in delivery of a sucrose pellet, while responses to the odors in the negative set (S-) were not reinforced. Training continued in this manner until the discrimination was mastered. A reversal learning procedure was then performed in which the odors that belonged to the positive set in the previous training session now belonged to the negative set and vice versa. Contingencies were repeatedly reversed until stability criterion was met. Repeated reversals were then conducted with three odors from each set being presented throughout the session, with the remaining odor from each class withheld until the end of the session. Symbolic substitution was defined by responding to the withheld stimuli on a probe trial in accordance with the reversed class members. Scientific rigor was established by repeating these reversals with probe trials for a minimum of eight replications for each rat. Proportion of correct responding on probe trials was significantly above chance ($p < .05$) for all 12 subjects, providing strong evidence of symbolic class formation. These results indicate that this procedure is a useful model to explore the neurobiological bases of symbolic behavior in rodents.

Disclosures: A.C. Williams: None. K.G. Quann: None. K.E. Bruce: 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. J. Galizio: 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.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.12/EE6

Topic: I.05. Working Memory

Title: Microdoses of the psychedelic 2,5-dimethoxy-4-propylamphetamine improved reward learning in the passive corticosterone mouse model of major depressive disorder

Authors: *M. NOBACK, M. M. FLESHER, A. L. HALBERSTADT, J. W. YOUNG;
Univ. of California San Diego, San Diego, CA

Abstract: Impairments in reward learning and effortful motivation are common behavioral features of major depressive disorder (MDD), and correlate with increased systemic cortisol. Increased cortisol levels in MDD can be approximated in rodents using corticosterone (CORT - a rodent analog of cortisol) passively administered via dissolving in drinking water. There is increasing evidence that psychedelic compounds may be able to ameliorate these features of MDD. We previously showed that the psychedelic compound 2,5-dimethoxy-4-propylamphetamine (DOPR) increased effortful motivation in mice at sub-hallucinogenic (microdose) levels in mice with low baseline motivation. In this study, we tested DOPR for its ability to alleviate the reward-related impairments induced by chronic CORT in mice. 64 mice (C57BL/6, 50% female) were baseline tested in touchscreen-based versions of the progressive ratio breakpoint task (PRBT, motivation) and probabilistic reversal learning task (PRLT, reward learning), counterbalanced, then given CORT in drinking water for three weeks. Mice were then administered DOPR at 0, 0.01, 0.1, or 1 mg/kg (within-subjects design) and assessed in PRBT and PRLT over the following four weeks. CORT treatment continued throughout testing, and DOPR was administered 30 minutes pre-test. CORT treatment suppressed breakpoint (a measure of effortful motivation, $F(1,60)=13.023$, $p<0.001$), as did DOPR in sham-treated animals ($F(1,60)=9.704$, $p<0.05$) at all doses tested. In the PRLT, CORT alone did not affect performance, but low doses of DOPR increased target win-stay ratio (a measure of reward learning, $F(1,60)=32.591$, $p<0.05$ at 0.01 mg/kg and 0.1 mg/kg), and all doses increased nontarget lose-shift ratio (a measure of punishment sensitivity, $F(1,60)=22.261$, $p<0.001$) in both CORT- and sham-treated animals. Motor effects of DOPR (measured by trials completed) were only seen at 1 mg/kg ($F(1,60)=22.186$, $p<0.001$). Microdoses of DOPR improved reward-related decision-making as measured by PRLT. These effects were seen irrespective of CORT pretreatment. Although hallucinogenic-related doses of DOPR impaired effortful motivation as measured by PRBT in control mice, microdoses could be beneficial in improving reward learning deficits. Currently, we are determining the reproducibility of these findings in control mice and in other MDD models, including acute physostigmine administration.

Disclosures: M. Noback: None. M.M. Flesher: None. A.L. Halberstadt: None. J.W. Young: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.13/EE7

Topic: I.05. Working Memory

Support: NIH R15 MH122935
NIH 3R15MH122935-01S1
NIH 3R15MH122935-01S2

Title: Barking up the wrong tree: Visual, not auditory, sensitivity differences in high schizotypy

Authors: *M. E. BERRYHILL¹, J. N. PABLO², L. L. KEMMELMEIER², W. TORRENS³, S. M. HAIGH⁴;

¹Psychology, Univ. of Nevada, Reno, NV; ²Psychology, ³Neurosci., ⁴Dept. of Psychology and Inst. for Neurosci., Univ. of Nevada, Reno, Reno, NV

Abstract: The relationship between sensory and working memory deficits across the schizophrenia spectrum is poorly understood, even in the auditory domain which is canonical in diagnosed schizophrenia. One approach to understanding the underlying mechanism(s) of schizophrenia spectrum disorders is to study neurotypicals, who vary in schizotypal trait load. Neurotypical participants provide insight at a smaller effect size, while avoiding recruitment challenges, side effects from medications, duration of disease, and psychosis. If sensory and working memory performance are related, identifying a sensory deficit might provide an accessible target for remediation, which would ideally improve upstream cognition. Previously, we found increased sensory sensitivity that positively correlated with higher schizotypy trait load, suggesting perturbed function is detectible in nonclinical participants. Here, we predicted we would observe worse sensory and working memory performance with higher schizotypal trait load. We designed a novel ‘Barking Dogs’ online paradigm testing sensory and working memory for similar auditory stimuli. 130 undergraduate participants heard two pairs of sequentially presented ‘barks’ separated by a short delay (200 ms; sensory memory) or a long delay (2000 ms; working memory). They reported whether the second and first pair matched (50% match). Mismatch trials were either the reordered initial pair (25%) or included a novel bark (25%). As a measure of visual sensitivity, we collected the Pattern Glare Test, a static horizontally oriented grating, and asked participants to report any visual illusions they experienced. Participants’ schizotypy trait load was quantified via self-report on the 32-item Schizotypal Personality Questionnaire - Brief Revised (SPQ-BR). The data revealed no auditory sensory or working memory deficits as a function of overall SPQ-BR score. Although, there was a significant positive relationship between SPQ-BR score and the number of illusions reported for the Pattern Glare Test (Spearman’s $\rho=0.33$, $p<.001$). We found no relationship between auditory sensory or working memory and schizotypy traits in our nonclinical sample. We replicated our finding of increased visual sensitivity with more schizotypy traits, demonstrating perturbed sensory functioning that does not appear to relate to (auditory) cognition, at least not in the high trait load sample. Further exploration into the effect of sensory sensitivity on schizotypy is warranted and calls for assessment across the sensory modalities.

Disclosures: M.E. Berryhill: None. J.N. Pablo: None. L.L. Kemmelmeier: None. W. Torrens: None. S.M. Haigh: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.14/EE8

Topic: I.05. Working Memory

Title: Working Memory Demands Influence the Balance between Detailed and Gist-Level Representations during Planning

Authors: *Z. YING¹, M. G. MATTAR³, A. KIYONAGA²;

¹UCSD, San Diego, CA; ²Cognitive Sci., UCSD, La Jolla, CA; ³Psychology, NYU, New York, NY

Abstract: Working memory (WM) is thought to support planning by maintaining representations of future actions and rewards. Our recent work examined choice behavior and WM for reward information in a planning context. We developed an information-theoretic model approximated by a variational recurrent neural network. Participants were asked to choose the best path in a decision tree where nodes were revealed sequentially and varied in value. After making their choice, they were also asked to recall the reward value of a subset of tree nodes. Both model and behavior showed better memory for nodes that were most informative for path selection, suggesting dynamic WM allocation based on choice-relevance. The model specifies that this allocation arises from limited WM resources, and predicts that higher WM demands would shift behavior toward prioritizing the overall decision quality rather than detailed path values. Here, we tested this idea. We manipulated WM load in two decision tree experiments, and we assessed the effects on choice behavior and node memory. In Experiment 1, we represented reward values by varying the node color, and we manipulated WM load by varying tree size and color-space resolution. In the larger-tree and higher-resolution conditions, recall relied more on overall path rankings than precise values, indicating gist-level encoding. In Experiment 2, we increased the number of reward-relevant features in the tree: both color and angle varied across nodes, but only one of those features determined the path value, which we cued at the end of each path. This was designed to examine planning when multiple action features contribute to plan quality, and to test how choice-relevance influences memory after encoding has already taken place. Recall was better for choice-relevant features, indicating a retroactive influence of choice on recall. Participants only showed this prioritization when they selected the path with the highest relevant feature value. In some cases where participants failed to select the correct path, they used simpler rules, such as choosing the path with the highest sum across both features or with the highest value from either feature. When those simpler rules pointed to a different path than the correct rule, participants' memory for relevant features did not improve. This result suggests that memory reflected planning heuristics. Across both experiments, higher WM demands were associated with more gist-level representations of plan quality and the application of satisficing planning strategies.

Disclosures: Z. ying: None. M.G. Mattar: None. A. Kiyonaga: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.15/FF1

Topic: I.05. Working Memory

Support: CSULB Research Foundation

Title: Stress induces affective working memory deficit for emotional facial expressions

Authors: *S. SAADE NEEDHAM¹, N. MARTIN^{2,1}, T. MURPHY^{2,1};

¹Psychology, California State Univ. Long Beach, Long Beach, CA; ²

Abstract: There is a substantial amount of evidence to suggest that stress plays a significant role in memory performance. Stress causes activation of the HPA axis which in turn releases glucocorticoids. Areas of the brain implicated with memory, such as the hippocampus and prefrontal cortex, contain a large number of glucocorticoid receptors. However, memory is not a unitary process, and stress seems to affect different aspects of human memory. This study investigated the effects of stress on working memory (WM), specifically, affective working memory (AWM). AWM is a specific type of working memory that maintains and manipulates emotional representations. Undergraduate students ($N=115$), both males and females from California State University Long Beach were randomly assigned to either the stress condition or the no stress control condition. In the pre-stress phase participants completed the 2-back WM task requiring recognition of 6 different facial expressions. These facial expressions included surprise, fear, anger, happy, sad, and neutral. The stress phase was either exposure to stress using the Maastrich Acute Stress Test (MAST) or no stress. The post-stress phase was the completion of a second 2-back task. AWM accuracy was assessed by the number of correctly identified emotions (percent accuracy) on the 2-back task. Results showed that accuracy on the 2-back task pre-stress did not differ between the stress and no stress conditions. However, post stress, the stress condition had significantly lower accuracy than the no stress condition. We further examined whether accuracy was affected by the type of emotional expression. Although there was no significant interaction between stress and facial expression accuracy, results did show a significant main effect of emotion, such that happy expression had better accuracy than any of the other emotions in both the stress and no stress conditions. Furthermore, surprise and fear had significantly less accuracy compared to anger, sad, and neutral expressions. These findings suggest that under stress, individuals may have a distorted or inaccurate representation of emotions. Furthermore, the disproportionately higher accuracy in recognition of happy expressions could imply that a happy expression may be enhanced by stress compared to other emotions.

Disclosures: S. Saade Needham: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.16/FF2

Topic: I.05. Working Memory

Title: Oxidative stress and ADHD: Fulvic acid mitigates ADHD symptoms and improves memory, mood, and anxiety in college-aged adults.

Authors: *C. B. ECKERSELL¹, M. RIDER², C. B. ECKERSELL², K. COLEMAN³, S. ROSSBERG³, P. ROSSBERG³, A. KEELE²;

¹Brigham Young Univ-Idaho, Rexburg, ID; ²Biol., ³Brigham Young Univ. Idaho, Rexburg, ID

Abstract: Elevated levels of oxidative stress have been linked to attention-deficit and mood-related disorders, an area of concern as these conditions become increasingly prevalent amongst young adults. Fulvic acid, known for its strong antioxidant and anti-inflammatory properties, may help mitigate the metabolic dysfunctions that underlie such mental health conditions. This investigation examined the efficacy of fulvic acid supplementation on attention, memory, anxiety, and depression symptoms in college-aged participants. A double-blind, placebo-controlled experimental design was employed, where participants completed validated self-report assessments over six weeks to assess changes in their mental health and ADHD-like symptoms. Memory performance was evaluated through a standardized word recall task, and attention was measured through a continuous conjunctive performance task (CCPT). Participants were gathered using a combination of purposive and convenience sampling from the BYU-Idaho undergraduate student population. Pre/Post analysis demonstrated statistically significant improvements across the mood and attention domains for participants in the treatment group (all $p < 0.001$), while placebo group changes remained non-significant (all $p > 0.10$). The treatment group achieved large effect sizes for ADHD symptoms (Cohen's $d = -1.10$) and medium effect sizes for anxiety and depression ($d = -0.70$), substantially exceeding placebo effects ($d = -0.29$ to -0.47). Linear analyses revealed progressive strengthening of treatment effects over time, with between-group effect sizes exceeding 1.0. However, analysis of the word-recall test data showed significant improvement over time regardless of condition, suggesting practice effects. These findings provide evidence for fulvic acid's utility in improving attention and mood. The magnitude of the improvements, particularly for ADHD symptoms ($d = -1.10$), positions fulvic acid as a promising natural supplement to reduce oxidative stress and neuroinflammation thus improving many aspects of brain function. Concurrent with these findings, we are investigating the molecular mechanisms that underlie these results.

Disclosures: C.B. Eckersell: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Necternal Labs. M. Rider: None. C.B. Eckersell: None. K. Coleman: None. S. Rossberg: None. P. Rossberg: None. A. Keele: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.17/FF3

Topic: I.05. Working Memory

Support: NMSS RG-1607-25467
UB SPARC Award

Title: Functional brain patterns distinguishing working memory cognitive training improvement in patients with multiple sclerosis

Authors: A. NGUYEN¹, D. W. SHUCARD², J. L. SHUCARD³, M. DWYER¹, T. J. COVEY⁴, *S. F. MULDOON¹;

¹Univ. at Buffalo, SUNY, Buffalo, NY; ²Neurol., Univ. at Buffalo, Neurol, Jacobs Sch. of Med. and Biomed. Sci., Buffalo, NY; ³Neurol., Univ. at Buffalo, Williamsville, NY; ⁴Univ. At Buffalo, Buffalo, NY

Abstract: In people with multiple sclerosis (MS), interventions to preserve and recover cognitive function are highly valuable. Cognitive rehabilitation through training on specific cognitive tasks has been suggested as one such intervention, with prior work demonstrating improvements on measures of cognition and well-being. However, the degree of improvement from cognitive training has proven to be heterogenous in MS patients. Efforts to understand cognitive training-related plasticity have yet to examine differences in brain connectivity as predictors. Brain connectivity patterns can provide insight into information processing in the brain, and can serve as biomarkers for both neuroplasticity and individual predictors of response to training. In this work, we describe neuroimaging analyses aimed at identifying functional connectivity patterns that are associated with, and predict, successful cognitive rehabilitation/training in patients with MS. Patients underwent a cognitive training program and were trained on either an N-back working memory task or a visual search task. Baseline pre-training resting state fMRI (rs-fMRI) in these training groups were used to train interpretable feed-forward deep learning prediction models to predict differences in pre-test post-test task performance. Weight analysis of acceptably performing models identified individual brain regions and pairwise connections between regions most associated with greater improvement. We found that cerebellar activity and connectivity is a strong predictor of training improvement across both training tasks, suggesting cerebellar involvement in the refinement of higher cognitive processes. More specifically, N-back accuracy improvement was predicted by the connectivity between default-mode network regions and other brain networks, which may reflect differences in individual cognitive reserve and the ability to suppress task-irrelevant processes. These baseline connectivity characteristics appear to facilitate efficacious training. Furthermore, these specific connectivity biomarkers can inform decisions on when and how to apply cognitive rehabilitation.

Disclosures: A. Nguyen: None. D.W. Shucard: None. J.L. Shucard: None. M. Dwyer: None. T.J. Covey: None. S.F. Muldoon: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.18/Web Only

Topic: I.05. Working Memory

Support: SECIHTI-CF-2023-G-597 to IDLPL
VIEP-BUAP2025 give to IDLPL

Title: Genetic Obesity Modifies Anxiety, Motor Activity, Memory, and Neuroinflammation

Authors: ***I. D. LIMON PEREZ DE LEON**¹, **A. PATRICIO-MARTÍNEZ**², **F. PATRICIO MARTÍNEZ**³;

¹Neuropharmacology Lab's, Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; ²Lab. de Neurofarmacología-FCQ, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico;

³Neuropharm. Laboratory, Sch. of Chem. Sci., Benemerita Univ. Autonoma de Puebla, Facultad de Medicina Veterinaria y Zootecnia, Puebla, Mexico

Abstract: Obesity is a chronic condition linked to metabolic dysregulation, neuronal alterations, and neuroinflammation in the brain. The obese Zucker rat is a widely used genetic model for investigating the neurological consequences of obesity. This study aimed to evaluate anxiety-like behavior, motor activity, short-term memory, and neuroinflammatory markers in obese Zucker rats (OZDF) compared to non-obese Zucker rats (LZDF) and Long Evans (LE) rats. Behavioral tests included the Elevated Plus Maze (EPM) for anxiety, the Open Field Test (OFT) for locomotor activity, and the Novel Object Recognition (NOR) test for memory. After testing, brains were collected for GFAP immunofluorescence analysis in the hippocampus and striatum. OZDF rats showed fewer entries into closed arms in the EPM, increased immobility and decreased movement in the OFT, and reduced exploration of the novel object in the NOR test. GFAP reactivity was significantly elevated in obese animals, suggesting enhanced astrocytic activation. These results suggest that genetic obesity alters emotional and cognitive behaviors and promotes neuroinflammation, highlighting the relevance of this model for studying obesity-related neuropsychiatric disorders. The valuable experimental participation of QFB Camargo Meneses Jessica and LF Díaz Luis Jovana is recognized. Thanks to support to SECIHTI-CF-2023-G-597 and VIEP-BUAP2025 give to IDLPL

Disclosures: **I.D. Limon Perez De Leon:** None. **A. Patricio-Martínez:** None. **F. Patricio Martínez:** None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.19/FF4

Topic: I.05. Working Memory

Support: P51OD011107 (CNPRC base grant; PI: Atkinson)
P51OD011107-62S3 (PI: Erin Kinnally)
R21AG081998 (PI: Erin Kinnally)

Title: Immune activation shapes working memory across development in rhesus macaques (*Macaca mulatta*) with evidence for inflammation related decline in novelty preference

Authors: ***B. CHAKRABORTY**^{1,2}, A. CRUZ², L. CENICEROS³, A. CUNNINGHAM², R. SUBEDI², A. BROWN², E. L. KINNALLY²;

¹California Natl. Primate Res. Ctr. (CNPRC), Univ. of California, Davis, Davis, CA; ²California Natl. Primate Res. Ctr. (CNPRC), ³Psychology, Univ. of California, Davis, CA

Abstract: We investigated how early-life immune factors shape cognitive trajectories across the lifespan in rhesus macaques (*Macaca mulatta*) using the Preferential Look test, a visual recognition memory task that measures novelty preference. This test measures recognition memory by recording the duration animals spend looking at novel versus familiar stimuli, with novelty preference reflecting better working memory and attentional engagement. In a large sample of younger animals (n = 4090) at the California National Primate Research Center, we matched immune markers, namely CD4, CD8 T cells, c-reactive protein, taken at 3-4 months of age with performance on the Preferential Look test conducted at the same age. Higher CD4 counts were associated with better cognitive outcomes, evidenced by increased novelty preference ($\beta = 0.61$, $p < 0.01$) and reduced inattention ($\beta = -2.99$, $p < 0.001$). Conversely, higher CD8 counts were linked to poorer cognition, showing lower novelty preference ($\beta = -0.50$, $p < 0.01$) and higher inattention ($\beta = 1.60$, $p < 0.01$). These findings suggest that robust immune activation, indicated by elevated CD4, supports working memory and social cognition early in life, whereas elevated CD8, characterized by their cytotoxic function, may reflect immune dysregulation and negatively impact cognition. Moreover, male macaques showed better working memory than females ($\beta = 0.04$, $p < 0.01$). Remarkably, we were also able to assess some of these same animals at 15-20 years of age (n = 9), providing a rare longitudinal perspective. In this older cohort, CD4 counts in infancy showed a negative association with novelty preference later in life ($\beta = -0.85$, $p = 0.02$), particularly among males ($\beta = -0.43$, $p < 0.05$), indicating that the relationship between immune function and cognition may shift with age, with males being affected more. CD4 and CD8 T cells play distinct roles in immune function, with CD4 cells supporting immune coordination and repair, which may aid cognition in early life, while CD8 cells mediate cytotoxic responses, which in excess may promote neuroinflammation and cognitive decline, particularly with aging. This unique longitudinal study offers valuable insights into how immune markers differentially influence cognition across developmental stages, highlighting potential mechanisms linking immune health and neural function over the lifespan.

Disclosures: **B. Chakraborty:** None. **A. Cruz:** None. **L. Cenicerros:** None. **A. Cunningham:** None. **R. Subedi:** None. **A. Brown:** None. **E.L. Kinnally:** None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.20/FF5

Topic: I.05. Working Memory

Support: SECIHTI CVU 1242590

Title: Working memory in university students

Authors: B. JIMÉNEZ¹, ***M. L. GARCIA-GOMAR**², A. NEGRETE¹;

¹Facultad de Ciencias de la Salud, Mexico, Mexico; ²FACULTAD DE CIENCIAS DE LA SALUD UABC, Tijuana, Mexico

Abstract: Objective: To assess working memory (WM) using both performance-based and self-report measures, identify the percentage of students with cognitive impairments, and determine the relationship between subjective cognitive failures and standardized scores on WM performance tests in university students. Participants: Forty-nine undergraduate psychology students (31 women, 17 men, and 1 non-binary individual), with a mean age of 20.3 ± 2.3 years, enrolled in the basic stage of their academic program. Instruments: The Cognitive Failures Questionnaire (CFQ) (Broadbent, 1982), the Working Memory subscale of the BRIEF-A (Behavior Rating Inventory of Executive Function - Adult Version) (Roth et al., 1996), and the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977). Procedure: Participants provided informed consent. The aforementioned instruments were administered over a 20-minute session. Raw scores were converted to T-scores for the BRIEF-WM and percentiles for the PASAT. Results: Students showed an average percentile score of 23.9 ± 23.1 on the PASAT, an average raw score of 45 ± 25.3 on the CFQ, and a mean T-score of 64.6 ± 10.8 on the BRIEF-WM. Depending on the instrument used, between 45% and 61% of students were identified as having WM impairments. A significant correlation was found between the CFQ and BRIEF-WM scores, but not with PASAT performance. Conclusions: Working memory impairments are a common issue among university students. When assessing WM in this population, it is essential to use a variety of measures, including both self-report instruments and performance-based tests.

Disclosures: B. Jiménez: None. M.L. Garcia-gomar: None. A. Negrete: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.21/FF6

Topic: I.05. Working Memory

Support: NYUAD Research Institute Grant CG012 (KKS)

Title: Uncertainty about future action modulates working memory

Authors: ***T. HRISTOVSKA**^{1,2}, K. RAAFAT^{1,2}, K. K. SREENIVASAN^{1,2};

¹Psychology, ²Div. of Sci. and Mathematics, New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: Flexible behavior relies not only on the information content stored in working memory (WM), but also on how that information is used to guide action. Memory is impaired when there is uncertainty about WM content, such as when memory load is high, highlighting the limited capacity of WM. However, it remains unclear whether uncertainty about how WM content will be utilized - that is, uncertainty about memory-guided actions - similarly impairs WM. When WM content has low uncertainty, as in tasks with low memory load, can uncertainty about future actions still interfere with behavior? We addressed this question by minimizing uncertainty about memory content using a task with a single memory item per trial while independently manipulating uncertainty about memory-guided action. We hypothesized that uncertainty about future action would impose behavioral costs even under low memory load. Participants performed a memory-guided saccade task that required them to maintain the location of a single target item in WM and, after a brief delay, make a saccade to indicate the target location. We varied the action participants used to report the target location: they were cued to either saccade to the target location (pro-saccade) or 180° from the target location (anti-saccade). Our key manipulation was varying the degree of uncertainty participants had about the upcoming memory-guided action: the shape of the target either indicated both the target location and the upcoming action with 100% validity (certain condition) or indicated the target location but was ambiguous as to whether the upcoming memory-guided action would be a pro- or anti-saccade (uncertain condition). In the uncertain condition, the specific action was only indicated at the time of report. Thus, in the certain condition, participants could link memory content to the intended action when the target was encoded into memory, while in the uncertain condition, memory content was encoded and stored without certainty about the intended action. We recorded gaze position throughout the experiment and analyzed saccade response times (RT) and memory error. As expected, average memory error was low, indicating that low uncertainty about WM content allowed for precise WM performance. In line with our hypothesis, memory error and RT were both increased for uncertain relative to certain trials, indicating that uncertainty about future action impairs WM behavior. Thus, even when uncertainty about the memory content was low, uncertainty about the upcoming action modulated memory-guided behavior. These findings support an emerging perspective that places future action as central to the function of WM.

Disclosures: T. Hristovska: None. K. Raafat: None. K.K. Sreenivasan: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.22/FF7

Topic: I.05. Working Memory

Support: R01 NS134754

Title: Mental Transformations & Motor Working Memory

Authors: *H. HILLMAN¹, T. MCCLURE², S. D. MCDOUGLE²;

¹Psychology, ²Psychology, Yale Univ., New Haven, CT

Abstract: Shepard and Metzler's groundbreaking 1971 study revealed a striking pattern: the greater the angular disparity between two 3D objects, the longer it took participants to determine whether they were identical. This finding suggests that mental rotation mirrors physical rotation. In the decades since, considerable research has examined the cognitive mechanisms underlying mental transformations, with a strong emphasis on the role of visual working memory. Yet, mental imagery is not confined to the visual domain. Sensorimotor recruitment during mental transformation tasks suggests that manipulation may be scaffolded by implicit motor computations. Here, we present findings that examine the link between mental rotation and motor-based, non-visual working memory, offering a new perspective on the cognitive architecture of mental transformations.

Motor working memory has been shown to encode movement information using both limb-specific and limb-independent (i.e., abstract) representations (Hillman et al., 2024). To investigate the interaction between mental rotation and motor working memory, we employed a dual-task interference paradigm. Participants first encoded a passively guided reaching movement. While maintaining this movement in memory, they performed a Shepard and Metzler-style mental rotation task. Subsequently, they were prompted to recall the reaching movement using either the same or the opposite arm. Because limb-specific information cannot support the recall of a non-mirrored movement when using the opposite arm, participants must depend solely on limb-independent representations to inform recall when using the opposite arm. This selective engagement allows us to dissociate the contributions of limb-specific and limb-independent representations within motor working memory.

We observed that increasing the angle of rotation in the mental rotation task leads to greater angular error during motor working memory recall. Furthermore, we found evidence that this interference differentially affects limb-specific and limb-independent representations. This suggests that the role of working memory in mental rotation is not restricted to the visuospatial domain, and supports the view that mental transformations leverage covert motor computations.

Disclosures: H. Hillman: None. T. McClure: None. S.D. McDougle: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.23/FF8

Topic: I.05. Working Memory

Support: UCSB Academic Senate Research Grant

Title: Geometric Context Modulates Systematic Biases in Human Spatial Working Memory

Authors: *D. LIM, T. C. SPRAGUE;

Dept. of Psychological & Brain Sci., UC Santa Barbara, Santa Barbara, CA

Abstract: Working memory (WM) enables the temporary storage and manipulation of information to guide behavior (Baddeley, 2010; Ma et al., 2014), with neural substrates spanning early visual cortex, parietal, and prefrontal regions (Christophel et al., 2017; Curtis & Sprague, 2021). Despite this distributed architecture, systematic biases often emerge during spatial WM tasks (Jiang & Leung, 2021). Recent studies have identified a key role for local visual environmental context in constraining allocentric spatial representations in medial temporal lobe structures, including the entorhinal cortex and hippocampus, in both covert and overt visual cognitive tasks in primates (Killian et al, 2012; 2015; Meister & Buffalo, 2018; Nau et al, 2018; Julian et al, 2018; Wilming et al, 2018). Critically, manipulations of the local visual environment sculpt the allocentric spatial encoding properties of single neurons and voxels measured in these structures. What role do these environmentally-anchored spatial representations play in biasing visual spatial WM representations? Here, we investigated how changes in the local visual environment, defined as a persistent screen aperture presented throughout each trial, impacted spatial WM performance. Participants performed a memory-guided saccade task, recalling the location of a briefly presented target dot presented within apertures of varying shapes (circle, square, horizontal/vertical rectangle) by making a saccade to the remembered location. We hypothesized that if local environmental context contributes to the scaffolding of visual spatial WM representations, aperture shape would induce systematic biases in memory. We found significant interactions between aperture shape and target location, indicating that recall error for each position depended on aspects of the local environmental context. These results are consistent with a prominent role for allocentric coding driven by changes in geometric context and suggest that local environmental geometry dynamically shapes the reference frames underlying spatial WM, supporting the view that the brain flexibly integrates allocentric cues from the environment to stabilize memory representations. By quantifying these geometric determinants of WM bias, our findings advance models of context-sensitive visual cognition and provide a behavioral framework for probing the neural mechanisms of visual reference frame transformation.

Disclosures: D. Lim: None. T.C. Sprague: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.24/FF9

Topic: I.05. Working Memory

Support: Alfred P Sloan Research Fellowship to TCS

Title: Serial dependence as a function of spatial working memory quality

Authors: *Y. LI¹, T. C. SPRAGUE²;

¹Univ. of California, Santa Barbara, Santa Barbara, CA; ²Psychological and Brain Sci., UC Santa Barbara, Goleta, CA

Abstract: Perceptual encoding of visual input is noisy and prone to a variety of biases. One such bias is serial dependence, in which our perception and working memory (WM) recall of visual stimuli is influenced by previously perceived stimuli (Fornaciai & Park, 2018; Fischer & Whitney, 2014), such that a current trial's perceptual or WM report attracted towards the previous trial's (Bliss et al., 2017). Serial dependence is thought to be a mechanism that helps us maintain a stable representation of the world by using the typical temporal continuity of our physical environment as a prior (Sheehan & Serences, 2022). A previous study demonstrated that trials with more robust neural representations of perceived orientations in visual cortex are less subject to serial dependence, suggesting that the relative quality of the current and past neural representations are important moderators of serial dependence (van Bergen & Jehee, 2019). Here, we tested whether the self-reported quality of visual spatial WM representations impacts the magnitude of serial dependence in a memory-guided saccade task. Participants remembered either one or two spatial locations on a screen, then were instructed to report either one cued location or the location they believe they remembered the best with a saccade towards the remembered location. Across several experiment variations (including confidence reports, variations in delay period, order of trials) we consistently observed attractive serial dependence between trials. Additionally, we found evidence that serial dependence magnitude was strengthened when participants reported their best-remembered item on the previous trial, consistent with previous results suggesting that serial dependence is the result of an inference process that integrates noisy representations of present and past experience based on the precision of visual information.

Disclosures: Y. Li: None. T.C. Sprague: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.25/FF10

Topic: I.05. Working Memory

Title: Neural Correlates of Olfactory Working Memory in Mice

Authors: *K. SHAW¹, A. R NAIR², S. PANDEY³, S. DAS², V. REGHUNATH², N. ABRAHAM⁴;

¹Biol., ²Indian Inst. of Sci. and Educ. and Research, Pune, Pune, India; ³Biol. department, Indian Inst. of Sci. Educ. and Res., IISER-PUNE, Maharashtra, India; ⁴Dept. of Biol., Indian Inst. of Sci. Educ. and Res. - Pune, Pune, India

Abstract: Abstract Title: Assessing Olfactory Working Memory in Mice Memory is the ability to encode, store, and retrieve information. Working memory (WM), a type of short-term memory, refers to the brief retention and modulation of information. Studies examining the neural correlates of working memory frequently employ rodents, using their highly developed olfactory system to investigate the mechanisms of olfactory working memory (OWM), in which odor information is retained for seconds to facilitate goal-directed behaviors. Previous studies from the lab had shown OWM deficits in long-COVID subjects. In this study, we present an optimized odor matching (OM) task to assess OWM in mice, where they compare two stimuli delivered at varying inter-stimulus intervals (ISIs). We observed a notable drop in OM accuracy between 16 and 20 seconds when presenting stimuli with pseudorandomized ISIs (4, 8, 16, 20, and 24 seconds). Mice also learned the mixed ISI task more slowly than the fixed ISI task. To investigate the role of olfactory bulb (OB) circuits in OWM, we measured c-Fos expression across different OB layers. The observed variations in c-Fos activity patterns suggest that OB circuits are involved in OWM. Additionally, to examine the causal relationship between OB circuits and OWM, we employed optogenetic inhibition in the GAD65+ interneurons of the OB, which resulted in the modulation of OWM and faster learning of om paradigm. further, we are studying the calcium dynamics across different ISIs while animals are involved in the olfactory matching paradigm.

Disclosures: K. Shaw: None. A. R Nair: None. S. Pandey: None. S. das: None. V. Reghunath: None. N. Abraham: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.26/FF11

Topic: I.05. Working Memory

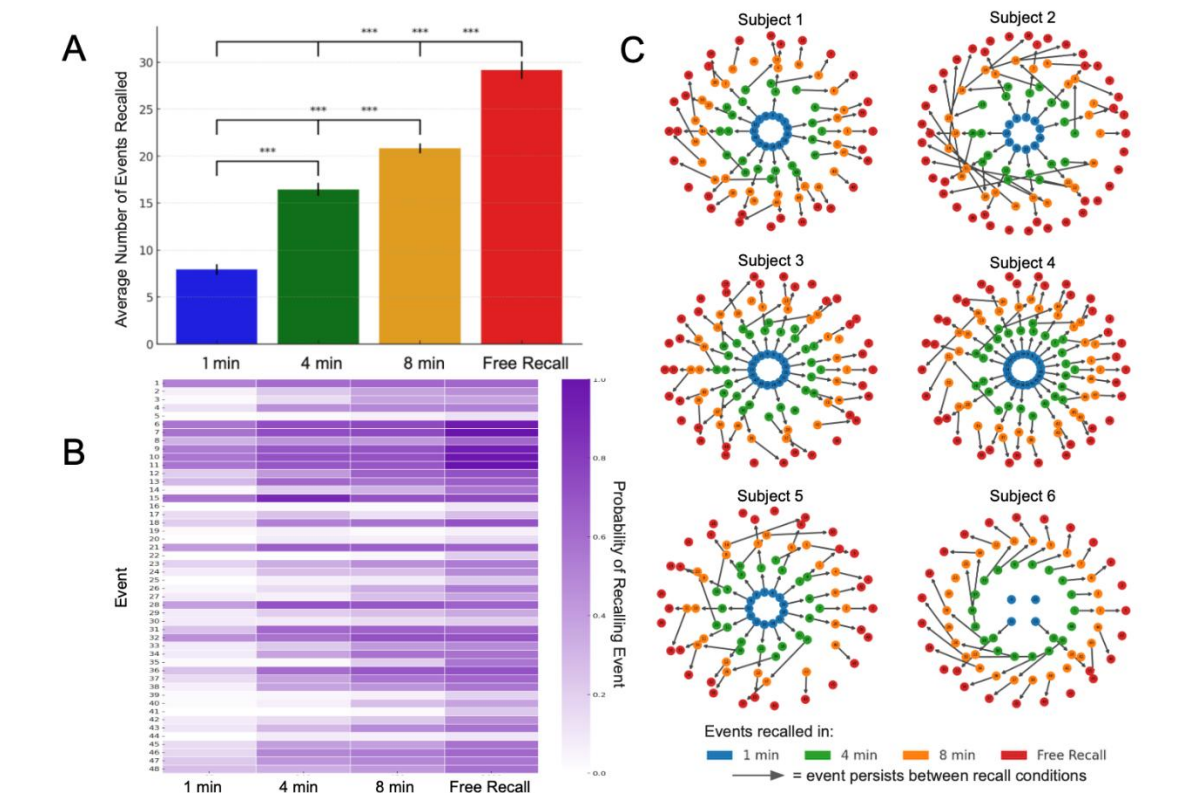
Title: Narrative Summarization Reflects Underlying Event Structure in Episodic Memory

Authors: *C. SUN¹, C. R. IORDAN²;

²Brain and Cognitive Sciences, Neuroscience, & Ctr. for Visual Sci., ¹Univ. of Rochester, Rochester, NY

Abstract: Humans frequently summarize complex experiences, a process that engages episodic memory retrieval, relevance-based content selection, and the construction of compressed, coherent narratives. Summarization is especially critical in naturalistic contexts, such as recounting a film or describing recent events. Despite its ubiquity and usefulness, the behavioral and neural mechanisms underlying summarization remain poorly understood. We hypothesize that summarization relies on assessing the informativeness of higher-order narrative structures, particularly events. Prior work shows that hippocampal activity peaks at event boundaries, and that the magnitude of these boundary responses predicts later memory reactivation and memory quality. This suggests a privileged role for events in tasks that engage episodic memory. Building

on this framework, we examined how event structure influences summarization of a naturalistic narrative. 32 adults from Rochester, NY viewed a 50-min episode of Sherlock and completed 4 recall tasks in counterbalanced order: untimed free recall, 8-minute constrained summary, 4-minute constrained summary, 1-minute summary. As temporal constraints on generating a summary increased, participants produced increasingly compressed responses that prioritized events central to the overall story structure ($p < 0.001$). Furthermore, event surprisal (T5) predicted which events were selected for inclusion in constrained summaries ($p < 0.001$), suggesting that unexpected or informative events disproportionately guide recall under time constraints. These findings highlight how humans leverage event structure to prioritize information sharing during summarization, reflecting an interaction between episodic memory and the compressed retelling of an experience. Our work sheds light on the cognitive architecture supporting summarization—an essential function for memory and learning in naturalistic environments. In an ongoing study, we are probing the neural mechanisms that afford efficient summarization of naturalistic narratives.



Disclosures: C. Sun: None. C.R. Jordan: None.

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.27/FF12

Topic: I.05. Working Memory

Support: PAPIIT-UNAM #IN221724

Title: Cognitive reserve as predictor of working memory performance

Authors: *E. LÓPEZ-GONZÁLEZ¹, *E. LÓPEZ-GONZÁLEZ², A. LÁZARO-FIGUEROA³, E. DE HARO HERNÁNDEZ², S. HERNÁNDEZ-MÁRQUEZ², I. GÓMEZ GONZÁLEZ⁴, S. LUCERO², D. GUERRERO LEON², U. CABALLERO SANCHEZ⁶, I. SANTOYO², M. ARIAS-GARCÍA⁷, A. RUIZ-CONTERARAS⁵;

²Facultad de Psicología, ¹Univ. Nacional Autónoma de México, Mexico City, Mexico; ³Facultad de Psicología, Univ. Nacional Autónoma de México, Mexico, City, Mexico; ⁴Facultad de Psicología, Univ. Nacional Autónoma de México, CDMX, Mexico; ⁵Facultad de Psicología, Univ. Nacional Autónoma de México, Mexico City, Mexico; ⁶Genómica computacional, Inst. Nacional de Medicina Genómica (INMEGEN), Mexico City, Mexico; ⁷UNAM, Mexico City, Mexico

Abstract: Cognitive reserve refers to the brain's ability to compensate for age-related or pathological changes, shaped by life experiences such as education, occupational demands, and engagement in cognitively stimulating activities. Prior studies have associated higher cognitive reserve with enhanced cognitive performance, particularly in domains such as working memory. The present study investigated the relationship between cognitive reserve—both overall and by individual components—and working memory efficiency. Forty-two right-handed adults (aged 20-55 years), free of neurological, psychiatric, or severe substance-use disorders, participated in the study. Participants completed a working memory task in which they attended to either letters or numbers, depending on the assigned condition, and determined whether the second attended item was hierarchically larger or smaller than the first. Cognitive reserve was assessed using a structured questionnaire measuring three components: educational attainment, occupational complexity, and engagement in leisure activities. Regression analyses revealed that total cognitive reserve, as well as the education and leisure activity components, significantly predicted task efficiency. In contrast, occupational complexity did not show any significant association with performance. These findings suggest that specific life experiences, particularly formal education and cognitively enriching leisure activities, may play a central role in enhancing working memory efficiency, offering insight into the differential contributions of cognitive reserve components.

Disclosures: E. López-González: 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.; 1083933 from the CONAHCYT. E. López-González: 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.; 1083933 from the CONAHCYT. A. Lázaro-Figueroa: None. E. de Haro Hernández: None. S. Hernández-Márquez: None. I. Gómez González: None. S. Lucero: None. D. Guerrero Leon: None. U. Caballero Sanchez: None. I. Santoyo: 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.; IN209024 (DGAPA-

PAPIIT-UNAM). **M. Arias-García:** 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.; IN218924 (DGAPA-PAPIIT-UNAM), PE304525 (DGAPA-PAPIIME-UNAM). **A. Ruiz-Contreras:** 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.; IN221724 (DGAPA-PAPIIT-UNAM).

Poster

PSTR042: Behavioral Studies With Working Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR042.28/GG1

Topic: I.05. Working Memory

Title: Diurnal behavioral outcomes and BBB integrity in adult male SHR and WKY rats

Authors: ***I. BIOSE**¹, P. SHRIVASTAVA², H. XIA³;

¹Cardiovascular Center of Excellence, LSU HSC -New Orleans, New Orleans, LA;

²Cardiovascular Center, LSU health sciences, New Orleans, LA; ³Cardiovascular Center of Excellence, LSU HSC- New Orleans, New Orleans, LA

Abstract: Motivation: Reduced spontaneous movement of Wistar-Kyoto rats (WKY) during neurobehavioral tests deems them less appropriate controls for Spontaneously Hypertensive Rats (SHR). However, a recent report shows that SHR and WKY exhibit comparable spontaneous activities at certain periods of the day and night. Hence, it is warranted to clarify whether there exists a diurnal difference in neurobehavioral test outcomes for SHR and WKY and to establish an optimal window for each test. In addition, it remains unclear whether young male SHR exhibit blood-brain barrier (BBB) dysfunction in brain areas related to cognition when compared to WKY, hence we determined whether there are potential strain-specific differences in BBB integrity. **Approach:** A total of fifty-three six months old male SHR (n=27) and WKY (n=26) rats were randomly divided into day and nighttime neurobehavioral test groups. Tests included: Y-maze spontaneous alternation, open field, novel object recognition, and tail suspension. BBB tight junction genes, histology, and function via FITC-Dextran permeability test were measured in the cortex, hippocampus, and striatum. **Results:** Blood pressure phenotype per strain was confirmed using terminal invasive carotid artery hemodynamic measurement. WKY rats showed significantly ($p<0.05$) higher recognition memory (RM) during the night compared to SHR and daytime test groups. Working memory (WM) and exploratory behavior were significantly higher ($p<0.05$) for SHR at both test times when compared to WKY. During the day and when compared to WKY, SHR showed significant ($p<0.05$) depression-like behavior which was absent during the night. SHR exhibited a higher ($p<0.05$) anxiety-like behavior at both testing times when compared to WKY rats. BBB function, tight junction genes and protein expressions were comparable between strains for all regions indicating that at six months of age, male SHR do not

show BBB dysfunction in brain regions pertaining to cognition. **Conclusion:** There is a time-of-day difference in outcomes for RM in WKY and for depression-like behavior in SHR. Regardless of time of day, male WKY rats are less exploratory than SHR, and SHR show a higher WM and anxiety-like behavior than WKY. The preserved BBB integrity in SHR explains our observation of higher memory.

Disclosures: I. Bioese: None. P. Shrivastava: None. H. Xia: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.01/GG2

Topic: I.07. Long-Term Memory

Support: NIH F32EY032352

Title: Stay tuned: Investigating neural representations in the presence of narrative context

Authors: L. GURGURYAN, H. GONZALES, *H. R. DIMSDALE-ZUCKER;
Univ. of California, Riverside, Riverside, CA

Abstract: Contextual regularities play a key role in how the brain represents information. To test this in a naturalistic-inspired lab-based task, we used real-world narratives (TV shows) to instantiate contexts and investigated how repeated exposure to these contexts influence the neural representation of associated stimuli (commercials). Using functional magnetic resonance imaging, participants (n = 33) completed three in-scanner tasks: (1) an initial n-back task in which they viewed 24 commercials to establish baseline neural representations devoid of contextual associations; (2) viewing of these same commercials embedded into episodes from eight different TV shows to instantiate contextual associations, and (3) a second n-back task with the same commercials to estimate changes in neural activity patterns following their contextual association with the TV shows. We used representational similarity analysis to quantify how representations of commercials shifted based on their contextual associations. This design enabled comparisons of commercials that were paired with (1) the same show, same episode; (2) the same show, but different episodes and (3) different shows. We hypothesized that different brain regions would represent these levels of contextual associations differently. Specifically, we hypothesized the hippocampus would be most sensitive to commercials linked within the same episode, whereas regions affiliated with helping to build general situational models of our ongoing context such as the posterior medial cortex and medial prefrontal cortex would integrate information across episodes of the same show. In contrast, we hypothesized that primary sensory areas (e.g., primary visual cortex) would be insensitive to contextual associations and instead reflect shared sensory-perceptual features of the commercials. Preliminary analyses revealed regional variations in the degree of representational strength between commercial pairs, regardless of their contextual association. Ongoing analyses aim to disentangle how these

contextual associations may differently modulate representational patterns across a priori regions of interest.

Disclosures: L. Gurguryan: None. H. Gonzales: None. H.R. Dimsdale-Zucker: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.02/Web Only

Topic: I.07. Long-Term Memory

Support: UNAM DGAPA PAPIIT IG300124

Title: Anxiolytic, antidepressant, and hypnotic effects on the accuracy and speed of accessing information from episodic memory

Authors: *S. CANSINO¹, F. TORRES-TREJO¹, C. ESTRADA MANILLA¹, S. RUIZ VELASCO ACOSTA²;

¹Lab. of NeuroCognition, ²Applied Mathematics and Systems Res. Inst., Univ. Nac Autónoma de México, Mexico City, Mexico

Abstract: The use of anxiolytics, antidepressants, and hypnotics to alleviate minor symptoms of anxiety, depression, and insomnia in the absence of any major disease has become extremely common. However, the effects of these medications are not completely understood. The aim of the present study was to examine the potential effects of these drugs on episodic memory, the ability to remember our personal experiences. In this study, we employed a computerized task that allowed us to measure recollection and recognition accuracy and speed within episodic memory. From a sample of 1656 participants between the ages 21 and 80 years, 87 had taken exclusively anxiolytics, 94 had taken only antidepressants, and 36 had taken only hypnotics at some time in their lives, but had not taken them for at least six months. These groups were compared with individuals who had never taken any of these medications and were matched by sex, age, and years of education. Recollection accuracy was lower in anxiolytics and antidepressants users compared with nonusers. In addition, we found that the longer and more frequently these drugs were taken, the worse recollection became. Recollection, one of the most essential memory processes to preserve autonomous everyday living, is affected by the consumption of anxiolytics and antidepressants, and this occurs across all ages in the adult life span.

Disclosures: S. Cansino: None. F. Torres-Trejo: None. C. Estrada Manilla: None. S. ruiz velasco acosta: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.03/GG3

Topic: I.07. Long-Term Memory

Support: National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (No. NRF-2021M3E5D2A01019538)
National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (No. RS-2024-00421203)
Alchemist Brain to X (B2X) Project funded by the Ministry of Trade, Industry and Energy (No. 20012355, NTIS: 1415181023)

Title: Hippocampal Theta Phase and Hippocampal Theta-Cortical Gamma Coupling Are Modulated by Auditory Alarm During Associative Memory Encoding

Authors: *S. LEE¹, C. CHUNG²;

¹Seoul Natl. Univ., Seoul, Korea, Republic of; ²Neurosci. Res. Inst., Seoul Natl. University College of Med., Seoul, Korea, Republic of

Abstract: In our previous research, an auditory alarm, given when the power of hippocampal theta oscillations fell below a prefixed threshold, enhances hippocampal theta power, thereby improving associative memory encoding performance. However, given that hippocampal theta phase coordinates phase-specific neuronal spiking activity and network-wide synchronization, the change on hippocampal theta phase with an auditory alarm needs to be studied. We hypothesized that auditory alarms delivered precisely at the hippocampal theta power trough selectively reset or modulate hippocampal theta phases, creating an optimal neural dynamic state conducive to successful associative memory encoding. We analyzed intracranial EEG data from seven subjects performing an associative memory task under three conditions: no alarm, random alarm, and theta-based alarm. First, hippocampal theta phase resetting was significantly stronger for successful memory encoding trials compared to failed trials in the no alarm condition. Additionally, both random and theta-based auditory alarms significantly enhanced hippocampal theta phase resetting in alarm-triggered trials compared to trials without alarms. Second, successful associative memory encoding was associated with increased phase-amplitude coupling (PAC) between hippocampal theta phase and cortical gamma power, compared to failed trials. While random alarms selectively enhanced PAC in the primary auditory cortex and right parietal cortex, theta-based alarms enhanced PAC not only in the primary auditory cortex and right parietal cortices but also extending into the left parietal cortex and fusiform gyrus. This extensive PAC effect of the theta-based alarms provides supports greater improvement in associative memory encoding observed under the theta-based alarm condition compared to the random alarm condition. Our findings provide clear evidence supporting our hypothesis that auditory alarms causally enhance hippocampal theta phase resetting and hippocampo-cortical theta-gamma coupling. Notable is the extensive enhancement of phase-amplitude coupling with theta-based alarms, across visual word processing cortical regions. In conclusion, auditory alarms could modulate hippocampo-cortical neural dynamics to enhance memory encoding and

highlights the substantial potential of theta-based auditory alarms as a targeted closed-loop neuromodulation strategy for associative memory enhancement.

Disclosures: S. Lee: None. C. Chung: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.04/GG4

Topic: I.07. Long-Term Memory

Title: Molecular and Cellular Representations of Social Discrimination of Novelty and Familiarity in Mice

Authors: *R. ISHIKAWA^{1,2}, T. TANIMIZU^{1,2}, K. SAKURAUCHI², S. KIDA^{1,2};
¹Grad. Sch. of Agr. and Life Sci., Univ. of Tokyo, Tokyo, Japan; ²Tokyo Univ. of Agr., Tokyo, Japan

Abstract: Social recognition memory contributes to the discrimination of novel and familiar mice. Mice form a social recognition memory of a juvenile mouse in the social recognition memory task. This social memory enables the discrimination of novel and familiar mice. Our previous studies showed that expressions of c-fos and Arc, markers of activity-dependent gene expression, were induced in the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), basolateral amygdala (BLA), and hippocampus (HP) following exposure to a novel juvenile mouse. Moreover, protein synthesis inhibition in these brain regions impaired long-term social recognition memory without affecting short-term memory, suggesting that gene expression in these brain regions is required for social memory consolidation. In this study, we tried to understand molecular and cellular mechanisms for social discrimination between novel and familiar mice in the social recognition task. We first compared the levels of c-fos expression, a marker of consolidation and reconsolidation, and Lys 48-linked ubiquitin, a marker of destabilization of retrieved memory, in brain regions when mice were exposed to a novel mouse and then 24 hrs later, to the same (familiar) mouse. Interestingly, c-fos induction was not observed in the HP, but was observed in the mPFC, ACC, and BLA, in response to re-exposure to the familiar mouse. In contrast, this exposure to the familiar mice increased the level of Lys 48-linked ubiquitin in the HP, mPFC, and ACC, but not BLA. Interestingly, these observations indicate that HP increases c-fos expression and Lys 48-linked ubiquitin in response to a novel or familiar juvenile mouse, respectively, but shows distinct molecular representations. These observations suggest that the c-fos expression and Lys 48-linked ubiquitin are markers of “novel mice” and “familiar mice”, respectively, in the HP. To further examine the roles of brain regions of social discrimination, we performed Arc/Homer1a catFISH. Significant activations of identical neural populations (Arc and Homer1 mRNAs-positive neurons) were observed in the HP and mPFC, but not in the ACC and BLA, when mice were exposed to a juvenile mouse

twice, at a 30-minute interval. These observations suggest that the HP and mPFC play a critical role in social discrimination of novelty and familiarity.

Disclosures: R. Ishikawa: None. T. Tanimizu: None. K. Sakurachi: None. S. Kida: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.05/GG5

Topic: I.07. Long-Term Memory

Support: R01 AG064247
F99 NS139537
R01 AG064247-04S1

Title: Hippocampal Subfield Volume is Associated with Relational Memory Performance in Periadolescent Development: Findings from the PRANK study

Authors: *M. K. RAMIREZ, A. M. HELLER-WIGHT, J. N. SEXTON, H. V. GHANNAM, A. F. WILHELM, E. A. ARMBRUSTER, V. S. PHATAK, D. L. MURMAN, D. E. WARREN;
Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: The hippocampus plays a critical role in memory formation, and this structure undergoes significant structural development during childhood and adolescence. Specifically, while total hippocampal volume reaches stability in early childhood, the volume of individual hippocampal subfields continues to change throughout periadolescence. However, the relationship between these volumetric changes and the maturation of hippocampal-dependent relational memory remains poorly understood. To address this gap, we utilized structural MRI and task data from the Polygenic Risk of Alzheimer's disease in Nebraska Kids (PRANK) study. Periadolescent participants ($n = 132$, mean = 10.11yr) completed a relational subsequent memory (RSM) task in which they were asked to remember pairs of items, and this was followed by a delayed recognition test for memory of the studied pairs. The structural MRI protocol was adapted from the Human Connectome Project (HCP) Development/Aging study and included a T2-weighted quasi-coronal slab orthogonal to the long axis of the hippocampus (voxel size = .4 x .4 x 2 mm; slices = 30). MRI data were preprocessed using the HCP minimal preprocessing pipeline software. Hippocampal subfield volumes were then calculated using the Automatic Segmentation of Hippocampal Subfields (ASHS) pipeline (Princeton atlas). Hippocampal subfields analyzed included the subiculum, *cornu ammonis* regions 1 (CA1) and 2/3 (CA2/3), and the dentate gyrus (DG). We compared subfield volumes across three performance-derived groups of participants (low, medium, and high) based on subsequent memory performance. A one-way ANOVA revealed a statistically significant effect of group on right CA1 values. Tukey's HSD post-hoc test indicated that high performers ($M = 849.46$, $SD = 65.43$) had significantly higher right CA1 values than low performers ($M = 766.22$, $SD = 118.07$), $p = .027$.

These findings suggest that specific hippocampal subfields, particularly CA1, may play a critical role in relational memory during periadolescence. By linking individual differences in memory performance to structural variation in the hippocampus, this study contributes to a more nuanced understanding of how hippocampal differences are associated with relational memory during development.

Disclosures: M.K. Ramirez: None. A.M. Heller-Wight: None. J.N. Sexton: None. H.V. Ghannam: None. A.F. Wilhelm: None. E.A. Armbruster: None. V.S. Phatak: None. D.L. Murman: None. D.E. Warren: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.06/GG6

Topic: I.07. Long-Term Memory

Support: NIA Grant R56AG068149
NIA Grant RF1AG039103

Title: Age-related differences in content-selective functional connectivity emerge at encoding but not retrieval

Authors: *S. MONIER¹, S. SROKOVA², N. SHAHANAWAZ¹, M. D. RUGG¹;

¹Univ. of Texas at Dallas, Richardson, TX; ²The Univ. of Arizona, Tucson, AZ

Abstract: Episodic memory retrieval involves content-selective reinstatement of neural activity. Less is known about whether patterns of content-selective functional connectivity (FC) at encoding are reinstated at retrieval, or whether connectivity patterns at encoding and retrieval differ with age. Using psychophysiological interactions (PPI) analyses, we examined content-selective FC during encoding and retrieval in a source memory task and whether these effects were moderated by age. Additionally, we examined whether content-selective FC at retrieval overlapped with the effects seen at encoding. During fMRI scanning, 24 younger and 27 older adults encoded words paired with images of scenes or objects. At retrieval, participants judged whether a test word had been studied and, if so, whether it had been paired with a scene or an object. Seed regions were identified by locating peak neural activity in regions showing category-selective reinstatement effects. Regions included scene-selective parahippocampal place area (PPA), medial place areas (MPA), and occipital place area (OPA), and object-selective lateral occipital complex (LOC), as well as anatomically defined anterior and posterior hippocampus. At encoding, scene-selective seeds exhibited greater FC with bilateral occipital cortex, lingual gyrus, and fusiform gyrus for scenes versus objects. LOC showed stronger connectivity with bilateral occipital cortex for objects versus scenes. These effects were greater in younger than older adults. At retrieval, scene-selective regions showed increased FC during accurate scene source judgements with left dorsal and inferior prefrontal cortex (PFC) and with

the superior parietal lobule. LOC showed object-selective FC increases with left intraparietal sulcus, bilateral precuneus, and supplementary motor areas. Anterior hippocampus showed scene-selective FC increases with dorsal PFC and the superior parietal lobule, and posterior hippocampus showed object-selective FC with the precentral gyrus, supramarginal gyrus, and anterior cingulate. None of these effects were moderated by age. Overlap analyses revealed that the MPA and PPA exhibited reinstatement of scene-selective FC, with both showing increased connectivity with left inferior PFC during encoding and retrieval, and, for the MPA, also with the left superior parietal lobule. These findings suggest that content-selective FC changes are moderated by age at encoding but not at retrieval. Moreover, partial overlaps in content-selective FC across encoding and retrieval provide novel evidence for connectivity-based reinstatement mechanisms underlying episodic memory.

Disclosures: S. Monier: None. S. Srokova: None. N. Shahanawaz: None. M.D. Rugg: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.07/GG7

Topic: I.07. Long-Term Memory

Support: NIH Grant R21AG071231

Title: Age invariant modulation of task-related functional connectivity during episodic memory retrieval

Authors: *A. KIDWAI¹, S. SROKOVA³, M. D. RUGG²;

²Ctr. for Vital Longevity, ¹Univ. of Texas at Dallas, Dallas, TX; ³The Univ. of Arizona, Tucson, AZ

Abstract: We examined the changes in functional activity associated with task-related modulation of fMRI BOLD activity during two tasks that required retrieval of differing mnemonic content. 24 younger and 23 older cognitively healthy adults completed an encoding task consisting of a series of concrete words denoting objects that, on different trials, were superimposed on images of scenes, objects, or pixelated backgrounds. The word-image pairs were presented at one of two locations (left or right side of the central fixation point). A scanned retrieval task then followed, employing studied and unstudied words as the retrieval cues. Participants performed two different retrieval tasks, which were organized into interleaved mini-blocks (4 per task). A cue presented at the onset of each block signaled the task requirement. In the background task, the requirement was to first judge whether each test item was studied or unstudied, and if studied, whether it had been paired with a scene, an object, or a pixelated image. In the location task, the old/new judgment was followed by the requirement to signal the location (left/right) of the word when it was studied. fMRI BOLD activity elicited by recognized test items was contrasted according to task block (background vs. location). Robust age invariant

univariate task effects were identified. These took the form of elevated activity in the background task in bilateral dorsolateral prefrontal cortex and right caudate head along with enhanced activity in the location task in bilateral supramarginal gyrus, right inferior temporal sulcus, right superior frontal gyrus, and anterior cingulate cortex. Using each region as a seed, psychophysiological interaction analyses (PPI) was employed to examine task-related modulations of functional connectivity. A plethora of reliable effects were identified, the most interesting of which took the form of a convergence of effects on the left superior parietal cortex for left and right dorsal lateral prefrontal cortex, and right caudate seeds for the background > location task contrast. There was no analogous convergence for the location > background task contrast. Together, the findings demonstrate a set of regional double dissociations in the effects of task on test items subjected to identical study conditions. The connectivity results suggest that the retrieval of relatively more detailed information (background vs. location information) is associated with increased engagement and interaction between regions that putatively belong to a fronto-striatal-parietal control network. Further research is needed to elucidate the functional significance of these findings.

Disclosures: A. Kidwai: None. S. Sroková: None. M.D. Rugg: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.08/GG8

Topic: I.07. Long-Term Memory

Support: R21DA051737
P30DA046345
K01DA051709

Title: Hippocampal Volume Loss and Memory Impairment in Opioid Use Disorder

Authors: *P. S. REGIER¹, D. MCKINSTRY¹, J. M. STEIN¹, N. HAGER¹, J. BARASH³, D. D. LANGLEBEN¹, P. MANZA⁴, N. D. VOLKOW⁵, C. E. WIERS², Z. SHI¹, W. A. KOFKE¹;
¹Univ. of Pennsylvania, Philadelphia, PA; ²Univ. of Pennsylvania, Philadelphia, PA; ³Veterans Home, Chelsea, MA; ⁴NIH, Washington, DC; ⁵NIH, Natl. Inst. On Drug Abuse, Gaithersburg, MD

Abstract: Preclinical studies demonstrate the ability of high-dose opioids (e.g., fentanyl) to produce neurotoxicity, including dose-related hippocampal injury, increased hippocampal glucose utilization, and seizure activity, with protective effects observed from naloxone and antiseizure medications. In humans, PET and ASL MRI studies have shown alterations in cerebral metabolism and blood flow under remifentanyl, and clinical data link opioid misuse to cognitive deficits, including amnesia and increased dementia risk. We tested the hypothesis that chronic opioid exposure is associated with reduced hippocampal volume and impaired episodic

memory in humans. Participants were individuals on stable medication for opioid use disorder (OUD; $n = 94$) and healthy controls ($n = 40$). All participants underwent MRI; a subset ($n = 28$) also completed episodic memory tasks. Hippocampal volumes were extracted using an Automatic Segmentation of Hippocampal Subfields tool and normalized by total intracranial volume. Analyses were conducted in R (base, lme4, stats, emmeans): ANCOVA assessed group differences, controlling for sex, age, and race; repeated-measures, mixed-effects modeling tested whether hippocampal volume and group predicted recognition memory performance. The OUD group showed significantly reduced hippocampal volume bilaterally (left: $F(1,124) = 17.9$, $p < 0.001$; right: $F(1,124) = 18.4$, $p < 0.001$). Among the memory-tested subgroup, accuracy did not differ between groups ($t(26) = 0.51$, $p = 0.61$), however OUD participants exhibited slower reaction times ($t(26) = 2.09$, $p < 0.05$). The mixed-effects model revealed a significant interaction ($F(1,45) = 4.44$, $p < 0.05$), indicating that greater hippocampal volume significantly predicted better memory performance in the control group ($b = 0.51$, $p < 0.05$), but not in the OUD group. These findings show that individuals with OUD have significantly reduced hippocampal volumes relative to controls, consistent with preclinical evidence of opioid-related limbic system injury. In controls, hippocampal volume was positively associated with memory performance, a relationship that was absent in the OUD group, suggesting a decoupling of structure and function. Overall, these results may support emerging evidence linking chronic opioid exposure to memory deficits and increased dementia risk.

Disclosures: P.S. Regier: None. D. McKinstry: None. J.M. Stein: None. N. Hager: None. J. Barash: None. D.D. Langleben: None. P. Manza: None. N.D. Volkow: None. C.E. Wiers: None. Z. Shi: None. W.A. Kofke: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.09/GG9

Topic: I.07. Long-Term Memory

Title: Relationships between perceptual similarity, memory precision, and bias in location memory judgments

Authors: *L. R. PEZANKO¹, M. HOU¹, M. D. RUGG²;
²Ctr. for Vital Longevity, ¹Univ. of Texas at Dallas, Dallas, TX

Abstract: Attraction is a memory bias in which memory test items are judged to be more similar than they really are, whereas repulsion refers to the reverse situation. These biases seem to depend on the degree of perceptual or conceptual overlap between the items. Here, we examined relationships between perceptual similarity, memory precision and attraction/repulsion in long-term memory. A sample of healthy young adults ($N = 45$; age range = 18-35, 34 female) completed the experiment. Image triplets (2 members of which were presented at study, with the third employed as a lure at test), comprising images depicting objects drawn from a common

semantic category (e.g. chairs), were selected based on perceptual similarity as defined by the VGG16 convolutional neural network. The triplets were segregated by perceptual similarity into low, medium, and high sets. An additional set of medium similarity images, where the objects were drawn from different semantic categories, was also employed. At study, participants viewed 64 unique object image pairs where each pair member was presented on a virtual circle separated by 100° visual angle under the instruction to remember each image and its location. At test, studied images and lures were presented on separate trials. For each image, participants first recalled its studied location, signaling the location with an adjustable cursor, and then judged the object as “old” or “new”. Memory precision was defined as the inverse of the angular distance between the recalled and the studied location. Item discriminability (Pr) was quantified as the difference between hit rate and false alarm rate. Location judgments for correctly detected study items were segregated into ‘location hits’ (of variable precision) and ‘guesses’ by the application of a mixture model comprising rectangular (guesses) and Von Mises (location hit) distributions. As the similarity of the test images increased, Pr and memory precision declined. For medium and high similarity images, both location judgments categorized as guesses ($\geq 38^\circ$) and low precision ($20^\circ - 38^\circ$ error range) location hits demonstrated an attraction effect (a bias toward the studied location of the image’s pairmate). Importantly, when precision increased, this bias diminished significantly for high similarity images and was reduced to the chance level when error was $\leq 3^\circ$, regardless of similarity. Together, these findings indicate that the attraction effect is driven largely by image similarity but diminishes as precision improves.

Disclosures: L.R. Pezanko: None. M. Hou: None. M.D. Rugg: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.10/GG10

Topic: I.07. Long-Term Memory

Support: NRF Grant 2023R1A2C2005587
Samsung Electronics Co., Ltd. Grant A0426-20220108
NRF Grant RS-2024-00342897

Title: Individual differences in how depressive symptoms and stress influence episodic memory in middle-school and high-school students

Authors: *S.-E. PARK¹, K. CHOI¹, H. KANG¹, Y. RAH², S. LEE²;
²Dept. of Brain and Cognitive Sci., ¹Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Episodic memory is a hippocampal long-term memory function that binds together “what”, “where”, and “when” information, comprises different neural underlying mechanisms and different contributions to individual differences in learning and memory. The effect of stress on hippocampal episodic memory is particularly important in students, whose mental health and

individual susceptibility to stress during learning are factors widely known to affect school performance. We explored individual differences in episodic memory in middle and high school students and assessed their memory with respect to a self-reported depression scale (CES-D). We applied two stress conditions (social, time) to test susceptibility to specific types of stress on memory. In Experiment 1, 62 students (mean age 15.5) navigated through a virtual maze while passing 6 different objects along the way. During retrieval, the students were asked to choose the object that they saw (“what”), the location of an object (object-space memory, “where”), or the temporal order of two objects (“when”). Half of the trials were performed under social stress, in which three adult observers appeared on screen to “monitor” the students. Depressive students tended to perform worse in “where” memory, converging with the previous findings that depression patients often miss contextual details. Interestingly, we found that students with modest depression symptoms (but not “none” or “severe”) improved in “where” memory under social stress. The stress-dependent improvement was greater in middle school students, indicating varied outcomes of stress depending on mental health and development. In Experiment 2, 66 students (mean age 16.1) performed the “where” memory task in the fMRI scanner. As in Experiment 1, object-scene memory was better in the social-stress condition for students with moderate depression symptoms. Next, we found that increased activity in the right amygdala induced higher activation in the left hippocampus during the social-stress condition, and this elevated activation mediated the improvement in object-space episodic memory binding.

Disclosures: S. Park: None. K. Choi: None. H. Kang: None. Y. Rah: None. S. Lee: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.11/GG11

Topic: I.07. Long-Term Memory

Title: Theta oscillations (3-8 Hz) facilitate flexible coordination between the parietal and frontal cortices to support post-retrieval processing of episodic memory retrieval

Authors: E. F. GIBBENS¹, *E. NYHUS²;

¹Neurosci., ²Psychology and Neurosci., Bowdoin Col., Brunswick, ME

Abstract: Top-down control of episodic memory retrieval is a complex cognitive process which requires the dynamic coordination between frontal, parietal, and hippocampal regions. While previous research has suggested that theta oscillations (3-8 Hz) facilitate the interactions within this functional network (Nyhus & Curran, 2010), their specific role in supporting different phases of the retrieval process remains unclear. To address this, we examined the direction of information flow during an episodic memory retrieval task designed to engage cognitive control, aiming to dissociate the involvement of theta oscillations in pre-retrieval and post-retrieval processes. We recorded scalp EEG from 13 healthy adult subjects completing a verbal recognition memory and source retrieval task. Using partial directed coherence (rPDC), a

measure of directed connectivity, we evaluated the strength, timing, and direction of information flow between neural sources. Source localization was improved by obtaining 3D scans of each subject's head, enabling us to record individualized scalp electrode positions. Preliminary results revealed directed flow at theta frequency late into the retrieval process (600-1100 ms) from the right/left precuneus in the parietal cortex to the right middle frontal gyrus. Notably, this directed flow was stronger ($p < 0.05$) when the retrieval of source information was not required, suggesting that theta oscillations are involved in post-retrieval mechanisms, but not necessarily post-retrieval monitoring or selection. These findings build on prior research indicating dominant parietal-to-frontal theta flow during episodic memory retrieval (Anderson et al., 2010; Das & Menon, 2021) and provide new evidence that theta-mediated connectivity may support post-retrieval processes. Future efforts should explore the relationship between connectivity at theta frequency and various behavioral measures, including memory accuracy and confidence, to further clarify the role of theta oscillations. By examining oscillatory dynamics, this research advances our understanding of the networks underlying episodic memory retrieval and provides new insights into the mechanisms of cognitive control and coordination across different brain regions.

Disclosures: E.F. Gibbens: None. E. Nyhus: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.12/GG12

Topic: I.07. Long-Term Memory

Title: How do temporal expectations influence memory for complex narratives and events?

Authors: *A. JAYAN¹, W. LI¹, C. R. IORDAN²;

¹Neurosci. Grad. Program, ²Brain and Cognitive Sciences, Neuroscience, & Ctr. for Visual Sci., Univ. of Rochester, Rochester, NY

Abstract: The ability to perceive and remember naturalistic narratives is a cornerstone of human experience. One way we encode complex multimodal stories into episodic memory is through segmenting them into distinct events. In a narrative, a boundary between events is engendered by a change in topic, location, time, protagonist, or goals (*Kurby & Zacks 2008*). At event boundaries, neural activity in the hippocampus increases, and the magnitude of this increase is correlated with later memory quality and with later cortical reinstatement of the memory during recall (*Baldassano et al. 2017*). Contextual knowledge can both improve episodic memory and facilitate segmentation of narratives into canonical events (*Newberry & Bailey 2019*). However, it remains unclear whether anticipating the specific length of an experience affects how we perceive and remember it, especially in naturalistic contexts. To address this question, we ran a pilot experiment where we asked participants to watch either 5- or 20-min clips from the first episode of the TV show *Sherlock*. One group of participants (n=26) was informed beforehand of

the length of the video they would watch, while the other group (n=28) was not given this information. During viewing, participants identified events via keypress. Afterwards, they freely recalled the content of the clips and completed a questionnaire that probed their detailed knowledge about each canonical event in the narrative. We predicted that knowledge of the temporal length of the narrative to be experienced would result in faster reaction times for event segmentation, increased memory for individual events, greater semantic similarity between recall and the clip's script, and increased memory for fine-grained details. Participants' response times for identifying canonical event boundaries indicated a trend for a normative effect of temporal context; participants who were informed about the length of the clip identified events closer to canonical events (faster anticipation of event boundary: $p=.050$; faster response time for boundary occurring: $p=.076$). Additionally, the semantic content of participant recalls showed a trend towards earlier events in the narrative being remembered less similarly to their corresponding narrative script when participants anticipated a 20-min clip ($p=.064$), compared to when participants were agnostic about the upcoming length of the 20-min clip. Overall, our results suggest that temporal expectations related to the length of engagement with a naturalistic narrative may influence how people segment the narrative into events and may adjust the contents of the events from the narrative encoded into episodic memory.

Disclosures: A. Jayan: None. W. Li: None. C.R. Iordan: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.13/GG13

Topic: I.07. Long-Term Memory

Support: The Peanut Institute - USDA
Brains and Behavior Grant

Title: Association between glycosylated hemoglobin and memory in middle-aged women with prediabetes

Authors: *S. K. FERNANDES¹, C. M. MCCARTHY², W. ELAMAD³, T. Z. KING⁵, R. G. FERESIN⁴;

¹Biol., ²Chemistry/ Nutr., ³Nutrition/Chemistry, ⁴Nutrition/ Chemistry/Biology, Georgia State Univ., Atlanta, GA; ⁵Sch. of Nursing, Professor, Emory Univ., Atlanta, GA

Abstract: Cognitive decline in aging is influenced by a complex interplay of metabolic and neurological factors. In middle-aged women, prediabetes, as indicated by elevated glycosylated hemoglobin (HbA1c) levels, is associated with an increased risk of memory impairment. Early risk identification is essential to develop prevention strategies. Thus, the aim of this study was to evaluate the association of HbA1c and memory in middle-aged women with prediabetes. Middle-aged women with prediabetes (n = 13) underwent cognitive assessments and had their

HbA1c measured (DCA Vantage, Siemens Point-of-Care). Attention, short term memory, working memory, executive functioning, immediate and delayed recall and episodic memory were assessed using multiple cognitive function assessment including the Rey Auditory Verbal Learning Test (RAVLT), Wechsler Adult Intelligence Scale (WAIS)-IV Digit Span and Picture Sequence Memory via the NIH Toolbox. Pearson's correlation was used to evaluate the association between HbA1c and performance on various measures of memory. Statistical significance was defined as $p < 0.05$. HbA1c was significantly negatively associated with immediate verbal memory (RAVLT Trial 6; $r = -0.564$, $p = 0.05$) and delayed verbal recall ($r = -0.589$, $p = 0.04$), suggesting that elevated HbA1c may impair hippocampal-dependent memory processes. No significant correlations were observed between HbA1c and WAIS-IV Digit Span performance. Our preliminary findings indicate that elevated HbA1C levels may be inversely associated with hippocampal-dependent memory in middle-aged women. It may also imply that cognitive decline may begin earlier than traditionally understood; that is before the onset of type 2 diabetes. Targeting glycemic control in middle-aged women may be critical to the prevention and preservation of cognitive health as well as age related cognitive decline. Upon evaluation of other markers, we may extend this to multiple linear regression, a prediction model.

Disclosures: S.K. Fernandes: None. C.M. McCarthy: None. W. Elamad: None. T.Z. King: None. R.G. Feresin: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.14/GG14

Topic: I.07. Long-Term Memory

Support: NIH Grant R01 MH119099
NSF CAREER

Title: Neural origins of Persistent Mental Content

Authors: *G. KRESSIN PALACIOS¹, X. LI², Y. LAI¹, B. BELLANA³, C. J. HONEY²;
¹Dept. of Psychological and Brain Sci., ²Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; ³Dept. of Psychology, York University, Glendon Campus, Toronto, ON, Canada

Abstract: Some thoughts and experiences persist in our minds on the scale of minutes. This persistence can be beneficial, enabling us to find creative solutions to problems, but it can also be detrimental, leading to repetitive unwanted thoughts that are associated with depression and anxiety. What mechanisms underlie the persistent mental content? Our previous behavioral studies suggest mental persistence is driven by a slowly-changing “deep context” representation which biases memory retrieval towards significant recent experiences. Therefore, we set out to identify the neural correlates of this “deep context” process. We used fMRI to record neural activity in N=23 human participants before, during and after the induction of persistent content.

Persisting content was induced by listening to an immersive 11-minute spoken narrative. Before and after the narrative listening, participants generated chains of verbal free-associates. After listening to the narrative, the free-associate words were more highly related to the story. In a preliminary analysis, we then compared the neural activity associated with the generation of story-related and story-unrelated words. We observed increased activity in key nodes of the default mode network, including the retrosplenial cortex, angular gyrus, and precuneus. No increase in activity was observed in the hippocampus when story-related words occurred. Moreover, story-related words were not associated with increased BOLD signal in default mode network regions in the pre-story phase. These preliminary results implicate default mode network regions in the maintenance of a slowly changing “deep context”, which biases memory retrieval toward significant recent experiences.

Disclosures: G. Kressin Palacios: None. X. Li: None. Y. Lai: None. B. Bellana: None. C.J. Honey: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.15/GG15

Topic: I.07. Long-Term Memory

Support: NRF Grant (Global-LAMP Program) RS-2023-00301976
Creative-Pioneering Researchers Program at Seoul National University
(339-20240015)
NRF Grant RS-2023-00265406

Title: Effect of Semantic Association on Sequential Encoding of Words in Serial Recall Task

Authors: *H. YOO¹, B. C. LEGA³, S. LEE²;

²Dept. of Brain and Cognitive Sci., ¹Seoul Natl. Univ., Seoul, Korea, Republic of; ³Neurosurg., UT Southwestern Med. Ctr., Dallas, TX

Abstract: We examined how sequential and semantic associations affect sequential episodic memory, analyzing intracranial electroencephalography from 57 epilepsy patients implanted with depth electrodes in the medial temporal lobe (MTL). Subjects encoded ten consecutive nouns and later reconstructed their order by arranging them on a screen. Recall performance was quantified by the displacement of recalled serial position (SP) from the original. After preprocessing and excluding subjects with inadequate data ($n = 35$), we examined neural activity changes, theta phase reset, and phase-amplitude coupling (theta and gamma) during encoding in relation to recall performance. Theta phase reset and phase-amplitude coupling in the MTL are implicated in successful encoding of stimuli potentially via recruiting memory-selective cell groups modulated by the activity of a larger population. Behavioral analyses assessed the effects of SP and semantic similarity on item- and list-level

recall. Earlier SP ($t(12567) = 13.49^{**}$) and higher semantic similarity of a word to adjacent SPs ($t(12567) = -3.09^{**}$) contributed to higher item-level performance. However, overall semantic similarity across words in a list marginally predicted lower list-level performance ($t(1253) = 1.90^{\dagger}$) with significant modulation by list order ($t(1253) = -2.41^{*}$). This indicates that local semantic similarity supports serial recall, whereas global semantic similarity does not. We measured the effect of neural activity and its interaction with SP and semantic similarity on recall performance. After cluster level correction (threshold at one-sided $p < 0.05$), increased gamma power (> 50 Hz) in bilateral anterior hippocampus and left entorhinal/parahippocampal regions was associated with better recall performance during the latter half of encoding. Beta activity (10-35 Hz) decrease that is modulated by the effect of higher semantic similarity supported precise recall in bilateral anterior hippocampus within 300 ms of word onset. Theta phase reset in left anterior hippocampus coincided with increased gamma and was preceded by phase reset in left entorhinal/parahippocampal regions. Phase-amplitude coupling in left parahippocampus predicted better performance ($\beta = -0.12^{**}$). In summary, sequential coding seems to be driven by anterior hippocampus, and parahippocampal regions potentially provide contextual representation for each word presentation. Neural codes underlying serial recall for sequential and semantic associations seem to converge in anterior hippocampus via distinct timing- and frequency-specific activity.

Disclosures: H. Yoo: None. B.C. Lega: None. S. Lee: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.16/HH1

Topic: I.07. Long-Term Memory

Support: NRF RS-2023-00265406
NRF RS-2023-00301976
NRF 2023R1A2C2005587
Creative-Pioneering Researchers Program at Seoul National University
NRF RS-2025-02303740
NRF RS-2024-00452391
Mid-Career Bridging Program through SNU

Title: Complementary contributions of hippocampal subfields in the acquisition of object-context associations

Authors: *J. KIM, S. JEONG, J. KIM, J.-M. SEOL, I. LEE, S. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The hippocampus binds object representations with their spatial context to support episodic memory. Computational models suggest that the CA3/DG subfields are crucial for the

initial acquisition of associative memories, while the CA1 is important in later stages of memory. Here, we investigated how the CA3/DG and CA1 may differentially contribute to learning object-context associations in human memory. In the MRI scanner, 40 participants performed a navigation task in which they experienced two VR environmental contexts (forest/city) and four 3D objects (2 target objects per context). On each trial, they traveled on a linear track during which they intermittently stopped to encounter objects along the way (2 per outbound/inbound path) and asked to decide whether it belonged to that context. They received feedback immediately after the choice. Across 32 trials (16 in each context), they learned the target object-context associations by trial and error. Before and after the main task, participants also performed an object-detection task in which they viewed one object at a time on the screen. During acquisition, the neural activity patterns in the left CA3/DG became more similar for the objects paired with the same context than those paired with different ones. This was followed by a decrease in pattern similarity between objects associated with different contexts in the CA1 and subiculum. Interestingly, mPFC activity levels tracked the acquisition of object-context associations and increased in functional connectivity with the hippocampus across trials. Interestingly, the neural representation of each context (during navigation when no objects were present) became increasingly similar to that of the post-learning object-detection task (devoid of the context) specifically for the 2 target objects associated with that context, suggesting that CA1 encodes contextualized object representations through learning. Our findings demonstrate the complementary processes performed in the CA3/DG and CA1 in conjunction with the mPFC, as people learned to remember objects and their background context. In doing so, they inform existing computational models of memory by demonstrating the dynamics of human episodic memory acquisition across the hippocampal subfields.

Disclosures: J. Kim: None. S. Jeong: None. J. Kim: None. J. Seol: None. I. Lee: None. S. Lee: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.17/HH2

Topic: I.07. Long-Term Memory

Support: NRF Grant RS-2023-00265406
NRF Grant 2023R1A2C2005587
Global-LAMP Program of the NRF grant funded by the Ministry of Education RS-2023-00301976
Samsung Electronics Co., Ltd. Grant A0426-20220108
Creative-Pioneering Researchers Program at Seoul National University

Title: Impact of emotional abuse experience on adolescent hippocampal spatiotemporal memory network

Authors: *K. CHOI¹, J. MIN¹, J. CHA¹, D. CHUNG², S. LEE¹;

¹Seoul Natl. Univ., Seoul, Korea, Republic of; ²Biomed. Engin., Ulsan Natl. Inst. of Sci. and Technol., Ulsan, Korea, Republic of

Abstract: The hippocampus, the central region for spatiotemporal memory, undergoes protracted maturation until adolescence, with distinct developmental trajectories among its hippocampal subfields as well as connections with cortical regions. However, past studies show that normal cortico-hippocampal development is vulnerable, particularly to stress-induced alterations that ultimately contribute to an impairment in higher cognitive function. In 147 adolescents (mean age 14.44, 78 females), we investigated age-related differences in the hippocampal memory network and the effects of abuse (Korean version of Early Trauma Inventory Self Report - Short Form). We focused on emotional abuse (rather than physical abuse), which is known to have a greater impact and is more strongly linked to psychiatric symptoms. Neural activity was measured using fMRI while participants performed an episodic memory task that required them to remember what animals (what) appeared at which locations (where) in what order (when) on each trial. We found distinct patterns of memory performance and neural activity in adolescents with a history of emotional abuse (abused group) and those without such experiences (control group). First, the control group showed improvements in spatiotemporal memory accuracy with age. During memory encoding, significant hippocampal activation, particularly in the CA23DG subfield, was observed in the control group and remained high across development, whereas activation in other hippocampal subfields decreased over time. In contrast, the abused group did not show improvements in memory and exhibited lower hippocampal activation than the control group, and showed no specific age-related changes in subfield activation. When we looked at functional connectivity between the CA23DG and cortical regions, we found that the CA23DG and the left lateral orbitofrontal cortex increased in connectivity across development and was associated with episodic memory accuracy. A mediation analysis revealed that this connectivity mediated age-related improvements in episodic memory. However, this effect was not observed in the abused group, suggesting a moderating effect of emotional abuse on episodic memory development. These findings reveal a subfield-specific mechanism during memory encoding that supports the development of episodic memory in adolescence and provide insight into how emotional abuse may disrupt this developmental trajectory, possibly leading to impaired memory.

Disclosures: K. Choi: None. J. Min: None. J. Cha: None. D. Chung: None. S. Lee: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.18/HH3

Topic: I.07. Long-Term Memory

Support: National Research Foundation of Korea (NRF) Grant RS-2023-00265406
Global-LAMP Program of the NRF grant funded by the Ministry of

EducationRS-2023-00301976
National Research Foundation of Korea (NRF)2023R1A2C2005587
Creative-Pioneering Researchers Program at Seoul National University
339-20240015
Samsung Electronics Co., Ltd. Grant A0426-20220108

Title: Frontal Theta Correlates of Emotional Updating in Scene-based Episodic Memory

Authors: *M. KOO¹, S. LEE²;

²Dept. of Brain and Cognitive Sci., ¹Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Research shows that emotions become bound to spatial contexts and that those emotional memories can resurface when we return to those places. But what happens when a single location is linked to conflicting emotions? We explored the neural mechanisms behind this phenomenon in a group of 45 healthy participants (mean age: 28.9) using a scene-based emotional episodic memory task while recording their neural activity using scalp EEG. During encoding, each participant saw a neutral background scene, followed by two emotionally charged images (negative (N), positive (P), or neutral) overlaid onto the same scene in sequence. Single-emotion conditions consisted of two congruent emotions (N-N, P-P) and mixed-emotion conditions (N-P, P-N). Participants rated the emotional valence of each image on a scale from -3 to +3. At retrieval, only the neutral background scenes were shown without the emotional foreground object, and participants rated the emotional valence for each scene. Although valence ratings differentiated emotional from neutral scenes, in the mixed emotion condition, the second image was rated as less emotionally intense than single-emotion responses. Retrieval valence ratings also showed a significant difference across emotion conditions while viewing neural background scenes, indicating a successful emotion-context association. However, the valence of the background with mixed emotions showed a similar pattern to the neutral condition. In line with previous findings, EEG results revealed an increased early parietal theta activity (~500ms after stimulus onset) for emotional scenes compared to neutral scenes, reflecting detection of emotional significance. In the second emotion phase, mixed conditions elicited greater early frontal theta activity compared to single-emotion conditions. Notably, later frontal theta activity (1500-2100 ms) was correlated with the valence difference between the two scenes only in the mixed condition and mediated the relationship between the early frontal theta response and valence. These findings show that frontal theta oscillations may be dynamically engaged for both early detection of a change in emotional valence and late resolution of the emotional conflict for flexible updating of memory.

Disclosures: M. Koo: None. S. Lee: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.19/HH4

Topic: I.07. Long-Term Memory

Support: Research grant from the National Natural Science Foundation of China, #32100839
Research grant from the Human Frontiers Science Program, RGP 0062/2014
Research grant from Cao Guangbiao High Science and Technology Foundation, Zhejiang University, #2020QN002
STI 2030 - Major Projects, #2021ZD0200409

Title: Coexistence of cue-specific and cue-independent spatial representations in human retrosplenial cortex

Authors: *X. CHEN¹, Z. WEI¹, T. WOLBERS²;

¹Zhejiang Univ., Hangzhou, China; ²Aging, Cognition & Technol., German Ctr. For Neurodegenerative Dis., Magdeburg, Germany

Abstract: It is a fundamental question in spatial navigation research how different spatial cues are unified to form a coherent map of the environment. This study combined ultra-high-field 7 Tesla fMRI, desktop virtual reality, and a novel memory-dependent navigation paradigm. Participants visited four test locations arranged evenly along a linear track in predetermined sequences. At each location, they performed spatial judgments that relied on memory, using either landmark cues alone or visual self-motion cues (i.e., optic flow) alone. We employed two complementary approaches to detect positional coding: fMRI adaptation and representational similarity analysis (RSA). Both approaches revealed positional coding in the retrosplenial cortex (RSC) under each cue condition, but with distinct properties. For the adaptation-based positional coding, brain activation decreased as the distance between successively visited locations decreased. Adaptation-based positional coding was driven by the participant's true location and was cue-specific, meaning that multivoxel patterns of adaptation differed between cue types. In contrast, for the RSA-based positional coding, multivoxel activation pattern similarity increased as the distance between locations decreased. RSA-based positional coding was driven by the participant's self-reported location and was cue-independent, meaning that the spatial code generalized across cue conditions. Finally, although both codes followed similar spatial distributions along RSC's dominant connectopcy (i.e., its long axis), they were spatially dissociated at the voxel level. These findings suggest that distinct neural populations encode landmark information, self-motion information, and spatial memory representations independent of current sensory inputs. Taken together, this study for the first time demonstrates the coexistence of cue-specific and cue-independent spatial representations in the human RSC, suggesting that this region plays a crucial role in unifying diverse sensory inputs into coherent spatial representations in memory-guided navigation.

Disclosures: X. Chen: None. Z. Wei: None. T. Wolbers: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.20/HH5

Topic: I.07. Long-Term Memory

Title: Can memory precision explain how spatial and object overlap affects new learning across ages?

Authors: *S. KIM¹, B. CHALOUPKA², H. GONZALES¹, I. J. BENNETT¹, D. ZEITHAMOVA², H. R. DIMSDALE-ZUCKER¹;

¹Univ. of California Riverside, Riverside, CA; ²Psychology, Univ. of Oregon, Eugene, OR

Abstract: Similar prior experience can either facilitate or hinder new learning. Recent research in young adults suggests that whether prior information leads to memory facilitation or interference depends on the type of overlap (spatial locations vs. object identities). We hypothesized that memory precision may also determine the impact of prior experience, with more precise memory representations making it easier to resolve competition with novel, overlapping information irrespective of the type of overlap. We further predicted that these relationships may differ in healthy older adults given their known deficits in memory precision. To investigate this, younger and older participants learned object locations on a grid and then learned new grids that shared spatial locations or object identities with previously-learned grids. We found that both younger and older adults showed similar patterns: faster learning when spatial locations overlapped (facilitation) and slower learning when object identities overlapped (interference). Despite these overall parallels, older adults' representations of grid locations were coarser than their younger counterparts. Preliminary analyses in younger adults' indicate that an independent measure of memory precision predicted greater memory interference, specifically when there was overlap in object identities between prior and novel learning. This suggests that memory precision is not a unidimensional process, but rather its relationship with prior experience is complex and may be influenced by the nature of overlapping content.

Disclosures: S. Kim: None. B. Chaloupka: None. H. Gonzales: None. I.J. Bennett: None. D. Zeithamova: None. H.R. Dimsdale-Zucker: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.21/HH6

Topic: I.07. Long-Term Memory

Support: NIH 1F32AG071263
AA AARFD-21-852597
NIH R21-AG073973

Title: Plasma pTau217 predicts object location memory accuracy and memory precision in preclinical older adults and MCI within immersive virtual reality

Authors: ***T. T. TRAN**¹, E. JOHNSON^{7,2}, D. F. TADEO³, K. NGUYEN², L. DACORRO⁴, O. CHATZIFOTI⁸, A. D. WAGNER⁵, H. HOSSEINI⁶;

¹Stanford Univ., Palo Alto, CA; ²Psychology, Stanford Univ., Stanford, CA; ³Stanford Univ., San Francisco, CA; ⁵Dept. of Psychology, ⁶Psychiatry and Behavioral Sci., ⁴Stanford Univ., Stanford, CA; ⁷Psychology, Palo Alto Univ., Palo Alto, CA; ⁸Univ. of Athens, Athens, Greece

Abstract: Misplacing objects is a commonly reported clinical symptom that scales with disease severity in Alzheimer's disease (AD), suggesting a potential role of object misplacement as an early indicator of AD clinical symptoms. To quantify and track object misplacement, we utilized an immersive virtual reality task to examine both overall object location memory accuracy and precision for spatial location memory. Given the vulnerability of CA1 volume in both aging and AD due to early tau pathology, we hypothesized a key role of both pTau217 and CA1 function in both object location memory and memory precision.

Young adults (N = 27), clinically unimpaired older adults (N = 18), and patients with mild cognitive impairment (MCI) (N = 24), a transitional stage between healthy aging and AD, explored an immersive virtual environment (i.e., living room) using a headset-based virtual reality with movement tracking (HP Reverb G2 Omnicept). Participants learned the location of different objects within an immersive virtual environment and were tested on their location memory in both the immersive environment and a 2D map of the environment to test both egocentric and allocentric object location memory. In the egocentric version of the task, both clinically unimpaired older adults and adults with MCI demonstrated decreased object location memory accuracy and precision, relative to young adults. In the allocentric version of the task, only patients with MCI were impaired on the task compared to both clinically unimpaired older adults and young adults.

Critically, across both clinically unimpaired older adults and patients with MCI: (a) plasma pTau217 and plasma pTau217/A β 42 predicted egocentric and allocentric object location memory accuracy and memory precision, independent of clinical status, while (b) CA1 volume predicted performance in only MCI participants. These findings indicate a role for plasma biomarkers in predicting memory and memory precision in both clinically unimpaired older adults and patients with MCI. Furthermore, these results are the first to connect structural CA1 changes to object location memory deficits in patients with MCI, suggesting early AD-related memory deficits may be related to changes in hippocampal CA1 function.

Disclosures: **T.T. Tran:** None. **E. Johnson:** None. **D.F. Tadeo:** None. **K. Nguyen:** None. **L. Dacorro:** None. **O. Chatzifoti:** None. **A.D. Wagner:** None. **H. Hosseini:** None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.22/HH7

Topic: I.07. Long-Term Memory

Title: Musical Context Facilitates Event Segmentation and Sequential Learning Through Neural Network Reorganization and Strengthened Hippocampal Encoding

Authors: *Y. REN¹, T. I. BROWN²;

²Sch. of Psychology, ¹Georgia Inst. of Technol., Atlanta, GA

Abstract: Context profoundly shapes memory formation, yet how structured auditory contexts like music influence visual sequence learning remains unclear. We investigated how familiar music modulates neural mechanisms supporting temporal order memory using fMRI during statistical learning. Participants (n=89 behavioral, n=35 fMRI) learned probabilistic visual sequences paired with either familiar music or silence. During continuous image presentation, participants performed event segmentation while extracting sequential relationships, followed by retrieval practice testing sequence memory without music present. Behaviorally, music enhanced boundary detection accuracy ($F(1,1007)=18.742, p<.001$) and subsequent sequence recall ($t(86)=-2.292, p=.024$). Whole-brain analyses revealed reduced prefrontal and visual processing demands during music-accompanied learning, suggesting more efficient processing. ROI analyses demonstrated earlier and stronger boundary responses with music in hippocampus and inferior frontal gyrus, with their activity uniquely predicting memory performance in the music condition. Functional connectivity revealed striking network reorganization with music: enhanced MTL-vmPFC coupling replaced effortful frontal-parietal connectivity characteristic of control learning. Random forest modeling demonstrated that MTL-PFC-striatum connectivity patterns consistently predicted behavioral performance only in the music condition, indicating more reliable neural mechanisms underlying successful learning. Representational similarity analysis showed music enhanced within-sequence pattern similarity in hippocampal subfields (CA1, CA2, dentate gyrus) while reducing cross-boundary pattern separation demands. Classification analysis revealed more distinct positional coding in hippocampus during music learning. These findings demonstrate music can facilitate sequence learning through multiple complementary mechanisms: providing clearer contextual boundaries, engaging schema-based learning via enhanced hippocampal-vmPFC connectivity, and establishing consistent MTL-PFC-striatum circuits that reliably support memory formation. This reveals how structured contextual cues scaffold cross-modal learning with broad implications for educational and therapeutic memory enhancement applications.

Disclosures: Y. Ren: None. T.I. Brown: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.23/HH8

Topic: I.07. Long-Term Memory

Support: NIH Grant AG087366
Alzheimer's Association AARF-22-926755

Title: The Relationship between Memory Precision and Early Alzheimer's Pathology

Authors: *P. F. HILL, A. D. EKSTROM;
Univ. of Arizona, Tucson, AZ

Abstract: Episodic memory declines during healthy aging and is often reported as an early symptom of Alzheimer's disease (AD). Standardized assessments of memory performance are limited in their accuracy to predict progression of early-stage AD pathology, potentially missing out on subtle variations in the fidelity of details retrieved from memory. In the present study, 56 cognitively unimpaired (CU) older adults and 12 older adults with mild cognitive impairment (MCI) completed five study-test cycles of a continuous report item-location memory task. During the study phase, participants viewed trial-unique objects located around the perimeter of an invisible circle. During the test phase, old and new objects were presented in the center of the screen and participants were instructed to recall the original location of each object using a continuous response dial to indicate their response. Trial-wise distance errors between the remembered and true location of each object were fit with a probabilistic mixture model to estimate two model-based estimates of memory performance: retrieval accuracy (i.e., probability of a successful retrieval attempt) and memory precision (i.e., distance error variability among successful retrieval attempts). We also computed a model-free measure of memory precision as the average absolute distance error for both correct and incorrect retrieval trials. We acquired high resolution structural MRI data from a subsample of 55 participants (46 CU, 9 MCI) to examine associations between memory performance and medial temporal lobe (MTL) sub-regional grey matter volumes. We also obtained blood samples to measure plasma levels of beta-amyloid (AB42/AB40), phosphorylated tau (ptau-217), and neurofilament light chain (NfL). Model-free memory precision was significantly lower in MCI compared to CU; model-based precision did not significantly differ between the two groups. Hierarchical multiple regression analyses revealed that plasma measures of AB42/AB40 and NfL explained independent sources of variance in the model-free measure of precision. We also observed a significant association between model-free precision and left transentorhinal cortex volumes. By contrast, model-based estimates of memory precision did not significantly covary with any of the fluid biomarkers or MTL volumes. Whereas model-based measures of memory precision are based solely on successful retrieval trials, model-free estimates are inclusive of both successful and unsuccessful retrieval attempts. Our preliminary findings suggest that failing to account for unsuccessful memory attempts may overlook crucial indicators of early AD pathology.

Disclosures: P.F. Hill: None. A.D. Ekstrom: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.24/HH9

Topic: I.07. Long-Term Memory

Support: R01AG053555
R21AG075464
F32AG074621

Title: Impact of Alzheimer's pathology on hippocampal CA1 activation during statistical learning in older adults

Authors: *J. N. ADAMS¹, L. FISCHER³, N. MEZA², L. MCMILLAN⁴, J. R. BOCK¹, B. AVILA¹, D. TAYLOR², M. A. YASSA⁵;

¹Neurobio. and Behavior, ²Univ. of California, Irvine, Irvine, CA; ³DZNE, Magdeburg, Germany; ⁴Neurobio. and Behavior, UC Irvine, Long Beach, CA; ⁵Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Statistical learning (SL) is a form of implicit memory in which temporal regularities from the environment are extracted on rapid timescales, enabling generalization. This process is thought to be supported by the CA1 subfield of the hippocampus, relying on input from the entorhinal cortex (EC) via the monosynaptic pathway. Of the hippocampal subfields, CA1 is particularly vulnerable to tau accumulation in Alzheimer's disease (AD). However, whether emerging AD pathology impacts CA1 dysfunction during SL has not been tested. Here, we assessed CA1 and EC function during a SL task involving temporal regularities in cognitively unimpaired older adults with varying levels of AD pathology. We hypothesized that dysfunctional activation in CA1/EC would be associated with deficits in SL performance and related to AD pathology, particularly local tau pathology. Cognitively unimpaired older adults (N=27, 61-83 years old; 74% female) from the BEACoN study at UC Irvine completed hi-res (1.5 mm isotropic) SL task-based fMRI. The SL task involved triplets (A-B-C) of shapes that temporally co-occurred in a consistent sequence, intermixed with unpaired (U) stimuli with no predictable order. Implicit SL performance was measured by comparing response time to B stimuli, which are predictable after SL has occurred, to U stimuli. fMRI data was preprocessed in native space and the contrast between triplet versus U stimuli was quantified in first-level models. ROIs were generated using Automated Segmentation of Hippocampal Subfields (ASHS) applied to hi-res T2-weighted images. Activation was extracted for CA1, EC, and DG/CA3 (control region). EC tau and global amyloid- β (A β) pathology was measured with 18F-MK6240 and 18F-florbetapir PET, respectively. Higher CA1 ($r = 0.41$, $p = 0.03$) and EC ($r = 0.48$, $p = 0.01$) activation during SL trials was significantly associated with better implicit SL performance. There was no association between implicit SL performance and DG/CA3 activation, supporting the specific engagement of CA1 and EC during SL. Further, higher EC tau pathology ($r = -0.43$, $p = 0.05$) and global A β ($r = -0.45$, $p = 0.03$) were significantly associated with reduced CA1 activation during SL, with no relationship to EC or DG/CA3 activation. We demonstrate that CA1 function in older adults is related to implicit SL performance and is impaired by pathology in preclinical AD. These results suggest that tau pathology in EC may disrupt communication to CA1, leading to reduced CA1 activation and impaired implicit SL of temporal regularities. CA1 dysfunction and implicit SL performance may therefore be novel biomarkers of early AD pathological progression.

Disclosures: J.N. Adams: None. L. Fischer: None. N. Meza: None. L. McMillan: None. J.R. Bock: None. B. Avila: None. D. Taylor: None. M.A. Yassa: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.25/HH10

Topic: I.07. Long-Term Memory

Support: NIH R01-MH128552

Title: The interface of semantic and episodic memory in eye movements and hippocampal intracranial electrophysiology

Authors: *A. SAN AGUSTIN, J. L. VOSS, J. E. KRAGEL;
Neurol., Univ. of Chicago, Chicago, IL

Abstract: Saccadic eye movements guide the sampling of visual content during memory encoding. Human hippocampal activity is sensitive to episodic memory and to categories of visual stimuli, exhibiting distinct activity patterns for remembered versus forgotten items and for categories like human faces versus objects. This highlights the hippocampal role in integrating semantic and episodic information. However, it is unclear how semantic and episodic information interact to guide the behavioral expression of memory and whether this is accomplished by the hippocampus. In previous work, we demonstrated that higher recognition accuracy is associated with eye movement reinstatement during the test phase of an episodic memory task, which in turn is linked to the revisitation of previously viewed locations during the study phase (Kragel et al., 2021). Given that eye movements during the study phase are critical for successful memory formation, we aim to research their electrophysiological correlates related to different semantic categories in naturalistic scenes. To investigate this, we tracked eye movements and recorded hippocampal activity using intracranial EEG in human subjects with refractory epilepsy (N=6) as they performed an episodic memory task with scenes of distinct semantic categories. We examined changes in theta oscillation phase and fixation-locked event-related potentials (fERPs) to characterize content-specific hippocampal responses. Since fixations frequently occur in close succession, we used a deconvolution model to separate temporally overlapping neural responses and estimate the fERPs. Results revealed greater phase locking of theta oscillations immediately before and after fixations to people versus other visual categories and significantly greater fERP amplitudes for fixations on people (n = 544) compared to food (n = 824) and animals (n = 789) between 300-450 ms post-fixation, with peak differentiation at 363 ms ($F(2,10) = 8.855$, $p = 0.006$). These findings extend previous work by showing that the hippocampus exhibits content-sensitive activity time-locked to fixations during free-viewing of natural scenes, suggesting that the processing of visual concepts is likely a consequence of saccadic sampling. Such rapid responses may support the integration of semantic and episodic content, reflecting both what was viewed and when, thus, linking content-sensitive encoding with spatiotemporal context. Ongoing work aims to relate hippocampal activity to category-specific versus general eye movement patterns to disentangle the neuronal mechanisms underlying semantic and episodic spatiotemporal memory contributions to behavior.

Disclosures: A. San Agustin: None. J.L. Voss: None. J.E. Kragel: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.26/HH11

Topic: I.07. Long-Term Memory

Support: Swedish Research Council Grant VR 2019-02455

Title: The effects of episodic context and schema on memory integration

Authors: *Z. LIU, M. JOHANSSON, I. BRAMÃO;
Dept. of Psychology, Lund Univ., Lund, Sweden

Abstract: Information encountered across distinct events can be integrated in memory to support novel inferences. For example, seeing one person enter a house and later another person leave the same house may lead to the inference that they live together. Such integration can occur during encoding, when new experiences reactivate past ones, forming a unified memory trace, or during retrieval, through the flexible recombination of separately encoded memory traces. Both context and schema influence the encoding of our experiences. Episodic context supports memory by binding content and contextual information, while schemas embed new experiences within familiar knowledge structures. However, how episodic context and schema influence mechanisms of memory integration remains unclear. Specifically, how do shared encoding context and schema congruency influence the integration of overlapping events? To address this, we conducted two studies. Participants encoded AB and BC event pairs (sharing the B elements) and were later tested on indirect AC inference. In Study 1, AB and BC events were encoded in either the same or different episodic contexts. AC inference was tested with or without the original encoding context present. Results showed improved AC performance when the test context matched the encoding context, indicating that reinstated context facilitates retrieval-based integration. In Study 2, we used EEG-based multivariate pattern classifiers to examine reinstatement of context and schema during encoding and retrieval. Schema congruency was manipulated by presenting AB pairs in schema-congruent or incongruent contexts, while BC pairs appeared on neutral backgrounds. For schema-congruent events, inference was predicted by schema reinstatement during BC encoding, consistent with encoding-based integration. For schema-incongruent events, inference was predicted by context reinstatement during AC retrieval, indicating retrieval-based recombination of memory traces. These findings show that context enhances memory integration by facilitating access to related traces during retrieval, particularly when schema support is weak. In contrast, schema congruency promotes integration during encoding by activating prior knowledge that enables the formation of coherent, unified representations. Taken together, memory integration is flexibly supported by both retrieval and encoding mechanisms, depending on the congruency and availability of schema and contextual information.

Disclosures: Z. Liu: None. M. Johansson: None. I. Bramão: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.27/HH12

Topic: I.07. Long-Term Memory

Support: NSF IIS-2024633

Title: Distinct navigation strategies and entorhinal correlates of human path integration in immersive virtual reality

Authors: *A. S. TU¹, N. A. KROHN², M. J. STARRETT AMBROSE², C. E. STARK², M. HEGARTY³, E. R. CHRASTIL²;
²Neurobio. & Behavior, ¹Univ. of California, Irvine, Irvine, CA; ³Psychological & Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Episodic memory formation relies on integrating spatial and temporal contexts, a process often disrupted in aging and Alzheimer's disease. Our ability to navigate based on self-motion cues, or path integration, offers a window into how spatial information is encoded and retrieved. Path integration is commonly assessed using walking, immersive virtual reality tasks like Triangle Completion and Loop Closure. In Triangle Completion, participants estimate the direction and distance back to the starting point after walking two legs of a triangle. In Loop Closure, participants identify when they have returned to the starting point while continuously walking in a circle. Surprisingly, preliminary findings from 194 participants revealed weak correlations between these tasks, and self-reported strategies differed. Continuously updating the trajectory to the start location—a *homing-vector strategy*—was more effective for Triangle Completion, whereas summing path segments to locate the start—a *configural strategy*—yielded better results for Loop Closure. To explore these differences, 69 of these participants underwent fMRI scanning while viewing movement within a virtual room. This fMRI task measures grid-cell-like representations in the entorhinal cortex (EC), which are thought to provide the metric framework needed to build a global spatial map, supporting the use of configural strategies. Given the configural-strategy advantage in Loop accuracy, we hypothesized that EC grid-cell-like signals correlate more with Loop performance than Triangle, supporting the use of metric information for configural strategies. Alternatively, if EC grid-cell-like activity supports configural strategy use regardless of path integration accuracy, it may correlate more with performance in the Triangle task, where configural strategies were more commonly used. By examining the neural contributions to these path integration tasks, this study highlights how differences in the encoding and use of spatial information via distinct strategies may influence how spatial information (e.g., the memory of a traveled path) is stored and retrieved - ultimately providing insight into how spatial context supports episodic memory.

Disclosures: A.S. Tu: None. N.A. Krohn: None. M.J. Starrett Ambrose: None. C.E. Stark: None. M. Hegarty: None. E.R. Chrastil: None.

Poster

PSTR043: Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR043.28/HH13

Topic: I.07. Long-Term Memory

Support: Stanford Centre on Longevity
NIH Grant R01 AG065255
NIH Grant R01 AG074339

Title: Understanding the role of event boundaries in modulating learning and memory in healthy aging and preclinical Alzheimer's Disease

Authors: *S. SANKARASUBRAMANIAN¹, T. T. TRAN², E. C. MORMINO⁴, A. D. WAGNER³;

¹Stanford Univ., Palo Alto, CA; ²Psychology, Stanford Univ., San Francisco, CA; ³Dept. of Psychology, Stanford Univ., Stanford, CA; ⁴Neurol. and Neurolog. Sci., Stanford, Stanford, CA

Abstract: Young and older adults alike parse the continuous stream of information encountered in life into meaningful 'events' marked by event 'boundaries'. These event boundaries often represent shifts in the spatial and temporal setting (or context). Given the theorized role of event segmentation in effective learning and remembering, can we use contextually structured event boundaries, embedded in learning materials, to foster new learning in older adults and/or mitigate the effects of preclinical Alzheimer's disease (AD) on the acquisition and retention of new knowledge? Aging is marked by various structural and functional changes in the brain. These changes tend to have variable consequences for learning and memory. In this study, we have investigated how spatial and temporal shifts in context interact with age, brain connectivity, and AD pathology to modulate new learning and memory in older adults. Furthermore, we studied if test simple text-based induction of event boundaries in new learning material can mitigate age- and AD-related deficits, fostering better outcomes. PRELIMINARY RESULTS: On an initial sample of N=60, we find that the presence of spatial and temporal event boundaries in the textual learning materials promotes new learning in CU older adults. Ongoing analyses are being done to look at the role of AD biomarkers, including [tbc] plasma-based CONCLUSIONS: Findings from this study will help inform how spatial and temporal context based event segmentation is impacted in aging and disease, and how segmentation ability in turn impacts new learning and memory in older adults.

Disclosures: S. Sankarasubramanian: None. T.T. Tran: None. E.C. Mormino: None. A.D. Wagner: None.

Poster

**PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks:
Cellular, Network, and Behavioral Studies**

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.01/HH14

Topic: I.08. Learning and Memory

Support: IBS-R002-A1

Title: Differential Value Coding in CA1 and Medial Entorhinal Cortex

Authors: *M. SEO^{1,2}, J. KIM^{1,2}, M. JUNG^{1,2};

¹Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; ²Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Although the hippocampal formation is known to process value-related information, how different subregions work together to represent value remains unclear. In this study, we compared value-related activity in the medial entorhinal cortex (MEC) and CA1. We trained Wfs1-Cre mice in a classical conditioning task using odor cues associated with three levels of reward probability (0%, 25%, and 75%). During this task, we measured the activity of CA1 pyramidal neurons and MEC layer 2 pyramidal (L2P) neurons using in vivo calcium imaging. Both regions exhibited significant value signals, but three differences emerged. First, population activity in CA1 increased monotonically as a function of value, whereas MEC L2P neurons exhibited decreasing activity. Second, although both regions preserved similar value-dependent activity across the two cue sets at the population level, only individual MEC L2P neurons maintained consistent value-related responses, unlike CA1 neurons. Third, specific odor cue-selective responses were stronger in CA1 than the MEC L2P neurons. These differential activity patterns suggest that the two regions may employ distinct neural coding strategies to represent value. Future investigations into the functional interactions between these regions may reveal how value signals are organized and integrated within the MEC-CA1 circuit.

Disclosures: M. Seo: None. J. Kim: None. M. Jung: None.

Poster

**PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks:
Cellular, Network, and Behavioral Studies**

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.02/HH15

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG085288
NIH Grant MH123926

Title: Evidence for age-related vulnerability in dopamine-glutamate projections to the lateral entorhinal cortex

Authors: *J. N. TOMAIO¹, S. FLEURY³, A. BILDER¹, J. NACIMBA², L. ABHILASH⁴, Q. HA¹, O. GHAZY¹, I. CASTILLO¹, Y. KIM⁵, L. E. FENNO⁶, K. DEISSEROTH⁷, S. MINGOTE¹;

¹Neurosci. Initiative, CUNY Advanced Sci. Res. Ctr., New York, NY; ²Neurosci. Initiative, CUNY Advanced Sci. Res. Ctr., Bronx, NY; ³Psychological and Brain Sci., Dartmouth Col., Hanover, NH; ⁴Gill Inst. for Neurosci. and Dept. of Biology: Indiana Univ. Bloomington, Bloomington, IN; ⁵Stanford Univ., Palo Alto, CA; ⁶Psychiatry & Neurosci., Univ. of Texas at Austin, Austin, TX; ⁷Stanford, Stanford, CA

Abstract: Changes in neural connectivity are thought to be a fundamental cause of age-related cognitive decline. To support healthy brain function with aging, we must first identify the specific circuit alterations driving this decline. Episodic memory—the ability to recall distinct events and details—relies on the hippocampal formation, including the entorhinal cortex. The lateral entorhinal cortex (LEC), a main input to the hippocampus that processes the “what” component of episodic memory, is especially vulnerable to aging (Leal and Yassa, 2015). This vulnerability is linked to reduced novelty detection in older individuals (Reagh et al., 2018), yet the upstream neural mechanisms contributing to this LEC dysfunction remain poorly understood. Dopamine (DA) plays a key role in novelty detection and memory (Lee et al., 2021). A subset of ventral tegmental area (VTA) neurons co-release dopamine and glutamate (DA-GLU), forming the primary DAergic input to the LEC (Fleury et al., 2024; Lee et al., 2021). Our recent work (Tomaio et al., *in preparation*) used an INTRSECT viral strategy to label LEC-projecting DA-GLU neurons in young adult (3 months), middle-aged (14 months), and old (24 months) TH-Flp::VGLUT2-Cre mice, and revealed selective vulnerability of this DAergic subpopulation with aging. Old mice showed a significant decrease in tyrosine hydroxylase (TH) expression, suggesting impaired DA synthesis and release in this pathway.

To further address the functional impact of reduced TH expression, we combined optogenetic stimulation of DA terminals (ChRmine-oScarlet, Addgene 137161) with GRAB_{DA2h} photometric recordings (Addgene 140554) in the LEC of young (3-6 months), middle-aged (11-14 months), and old (≥ 24 months) DAT-IRES-Cre mice. Stimulation at 40 Hz for 60 seconds attenuated evoked DA release in old mice, consistent with a deficit in DA synthesis. We next tested whether photostimulation of DA terminals in the LEC of old mice could rescue the novel object recognition (NOR) deficit observed during the NOR behavioral paradigm. Closed-loop wireless optogenetic stimulation of DA terminals in the LEC (NeuroLux) during object exploration produced a modest but measurable improvement in novelty recognition performance. Together, these findings show that DA-GLU projections to the LEC are selectively vulnerable to aging at molecular and functional levels and suggest that this circuit could be targeted to reverse early impairments in novelty detection and memory.

Disclosures: J.N. Tomaio: None. S. Fleury: None. A. Bilder: None. J. Nacimba: None. L. Abhilash: None. Q. Ha: None. O. Ghazy: None. I. Castillo: None. Y. Kim: None. L.E. Fenno: None. K. Deisseroth: None. S. Mingote: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.03/III

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG085288

Title: Layer specific activation of the lateral entorhinal cortex to novelty and familiarity and the effect of aging

Authors: *M. MANSOUR¹, Q. HA², S. FLEURY³, S. MINGOTE¹;

¹Advanced Sci. Res. Ctr., CUNY Advanced Sci. Res. Ctr., New York, NY; ²Columbia Univ., New York City, NY; ³Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Layer-Specific activation of the lateral entorhinal cortex to novelty and familiarity and the effects of aging Manal Mansour¹, Quan Ha², Susana Mingote¹ *Abstract* The entorhinal cortex is the main cortical input to the hippocampus, making it a critical hub for relaying sensory information that supports memory updating and recall. The lateral entorhinal cortex (LEC), in particular, has been shown to respond preferentially to objects rather than spatial navigation (Sugar & Moser, 2019). The LEC is organized into six cortical layers. Human fMRI studies suggest that novel and familiar stimuli differentially activate these layers (Maass et al., 2014). However, the mechanisms underlying this layer-specific activation and how aging affects this process remain unclear. In this study, we used the FosTRAP mouse model to tag neurons activated during the initial exploration of a novel object with TdTomato fluorescent protein. Mice then underwent seven familiarization sessions with the same object. On the eighth day, animals encountered either a novel or familiar object and were perfused 1 hour and 30 minutes later to assess c-Fos expression. This approach enabled us to identify neurons activated by familiar or novel events. Control mice were exposed to the open field without objects. We found that novel object exploration selectively activated neurons in the superficial layers of the LEC compared to familiar object exploration or open field exposure. In contrast, activity in the deep layers was similar between the familiar object and open field conditions and was greater than the activation induced by novelty. We also examined reactivation of neurons by assessing colocalization between TdTomato and c-Fos. Colocalization was higher when animals encountered two different novel objects (at the first and second tagging time points), indicating that layer-specific activation is driven by novelty rather than object identity. Importantly, the layer-specific activation observed in young mice was lost in aged mice (24 months old), who also showed impairments in novel object recognition. We are currently reanalyzing these data using Ilastik and FastMap software to gain more precise information about which layers are differentially activated. These findings suggest that the LEC distinguishes between novel and familiar stimuli through layer-specific activation, a process that is altered by aging. This

highlights a potential mechanism by which sensory information is filtered to support memory, and how this process may degrade with age-related memory decline.

Disclosures: M. Mansour: None. Q. Ha: None. S. Fleury: None. S. Mingote: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.04/II2

Topic: I.08. Learning and Memory

Support: NIH Grant 1R21AG085288

Title: Dissecting the Role of Lateral Entorhinal Cortex in Memory Interference

Authors: *O. GHAZY¹, J. TOMAIO², S. MINGOTE³;

²Neurosci., ³Advanced Sci. Res. Ctr., ¹CUNY Advanced Sci. Res. Ctr., New York, NY

Abstract: Memory interference occurs when previously formed memories disrupt the acquisition or retrieval of new information. The latent inhibition (LI) paradigm has been used to study proactive interference. In this paradigm, a stimulus exhibits a reduced ability to form or express Pavlovian associations with another stimulus following non-reinforced exposure. The interference-based model suggests that LI arises because the memory that the pre-exposed stimulus is inconsequential interferes with the memory that it predicts a reinforcer. Prior lesion and inactivation studies using the LI paradigm implicate the entorhinal cortex in retrieving the memory that a pre-exposed stimulus is inconsequential (Coutureau et al., 1999; Lewis & Gould, 2007), suggesting a function in memory interference. The lateral entorhinal cortex (LEC) is associated with stimulus-related memory, and its function decays in aged individuals, who show increased memory interference (Leal & Yassa, 2015; Wilson et al., 2006). Thus, this study investigates the specific role of LEC in LI and proactive memory interference. Experiment 1 established parameters for a robust LI effect. This protocol included three days of pre-exposure to a 30-second tone (60 presentations total), followed by a conditioning day with three tone-shock pairings, and a retrieval test day in which the tone was presented for 6 minutes in a novel context. The control group was pre-exposed to a 30-second light instead of the tone. Using this design, we found that pre-exposed (PE) young males (n = 4) and females (n = 4) did not exhibit a fear response (i.e., freezing) during the retrieval test, indicating LI. In contrast, non-pre-exposed (NPE) animals displayed robust freezing to the tone presentation, consistent with a fear conditioning response. In experiment 2, we used a chemogenetic approach to transiently inhibit excitatory neurons in the LEC during the memory retrieval test day. Male and female mice (age 4 to 7 months, C57BL/6) received injections of either AAV9-CamKIIa-hM4D(Gi)-mCherry (n=12) or injections of the control virus AAV9-CamKIIa-mCherry (n=15) bilaterally into LEC. The injection of CNO (1mg/kg) before retrieval attenuated the LI effect in the PE DREADD

group but not in the mCherry PE group. CNO injection did not affect fear conditioning responses in the NPE DREADD or mCherry group. This attenuation in LI responding supports a role for the LEC in retrieval-based memory interference.

Disclosures: O. Ghazy: None. J. Tomaio: None. S. Mingote: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.05/II3

Topic: I.08. Learning and Memory

Support: NIMH, MH129970, PI: AJ Eisch
NIDDK, DK135871, PI: SA Zderic
NINDS, NS088555, PI: AM Stowe
NINDS, NS126279, PI: R Ahrens-Nicklas
NASA HERO Grant, 80NSSC21K0814, PI: S Yun
Foerderer Fund for Excellence, PI: Van Batavia
CHOP Jr. Faculty Pilot Grant, PI: Van Batavia

Title: Characterizing calcium dynamics of lateral entorhinal cortex fan cells during encoding and retrieval of a pattern separation task

Authors: *N. BABIKER¹, G. BANCROFT¹, E. DELLINGER¹, A. PATEL¹, A. J. EISCH², S. YUN³;

¹The Children's Hosp. of Philadelphia, Philadelphia, PA; ²Anesth & Crit Care and Neurosci, UPenn & CHOP, Swarthmore, PA; ³Anesthesiol. and Critical Care, Children's hospital of Philadelphia, Philadelphia, PA

Abstract: Behavioral pattern separation (BPS) - the ability to distinguish similar stimuli - is sensitive to memory “load” (increased stimuli similarity) and is separable by memory stage. BPS is altered in aging and neuropsychiatric disorders, with the entorhinal cortex (EC) to hippocampal dentate gyrus (DG) pathway playing a critical role in humans and rodents. Our pilot data shows inhibition during memory encoding decreases BPS at high load. Prior studies have also shown that reactivation of LEC cells tagged during encoding are necessary for successful retrieval of episodic-like memories. However, no studies have characterized the real-time activity of LEC fan cells, specifically those active in both encoding and retrieval (“overlap”/potential “engram”) during BPS, or how this activity differs with pattern separation difficulty. To advance our understanding of LEC fan cell involvement across BPS stages, we measured Ca²⁺ transients in LEC fan cells of awake, freely-moving mice using one-photon microscopy during encoding and retrieval phases of a BPS test using the spontaneous location recognition test (SLR). We hypothesized a subset of LEC fan cells could be identified as

overlapping between encoding/retrieval and would show greater activity with higher load. 8.5 wk-old Sim1-Cre mice (n=2 male, n=4 female) received infusion of AAV9-CAG-flex-GCaMP6f and GRIN lens implantation into the LEC. 9 wks post-surgery, mice underwent SLR (10-min encoding, 35-min delay/consolidation, 5-min retrieval) with identical sample objects placed in a dissimilar (d-SLR), similar (s-SLR), or extra similar (xs-SLR) location. These three “loads” are ranked in difficulty from easy (d-SLR) to very hard (xs-SLR). Ca²⁺ transients - indirect measures of cell activity - were analyzed at the single-cell level using published MiniAn and CellReg pipelines. Behavioral output was obtained with SLEAP/SimBA software. Overlapping neurons emerged between encoding/retrieval for each SLR load, composing 36-39.7% of the total identified neurons in a session. 28.2-33.8% of cells were encoding-specific and 27.9-33.3% were retrieval-specific. During encoding, Ca²⁺ signal intensity was lower with higher memory load in overlap cells. Retrieval specific cells had higher Ca²⁺ signal intensity with higher memory load. Interestingly, overlap cells showed significantly higher Ca²⁺ intensity (d, xs) and lower event rate (d, s, xs) in comparison to both encoding/retrieval specific cells, suggesting burst firing behavior. Further defining the activity of this circuit will provide insight into treatments for conditions marked by BPS impairment.

Disclosures: N. Babiker: None. G. Bancroft: None. E. Dellinger: None. A. Patel: None. A.J. Eisch: None. S. Yun: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.06/II4

Topic: I.08. Learning and Memory

Support: NIH F31 MH134582
NIH R01 MH119102

Title: A cortical-hippocampal communication undergoes rebalancing after new learning

Authors: *A. HALL;

Drexel Univ. Col. of Med. Neurosci. Program, Philadelphia, PA

Abstract: The brain's ability to consolidate a wide range of memories while maintaining their distinctiveness across experiences remains poorly understood. Sharp-wave ripples, neural oscillations that occur predominantly within CA1 of the hippocampus during immobility and sleep, have been shown to play a critical role in the consolidation process. More recently, evidence has uncovered functional heterogeneity of pyramidal neurons within distinct sublayers of CA1 that display unique properties during ripples, potentially contributing to memory specificity. Despite this, it remains unclear exactly how ripples shift the activity of CA1 neuronal populations to accommodate the consolidation of specific memories and how sublayer

differences manifest. Here, we studied interactions between the anterior cingulate cortex (ACC) and CA1 neurons during ripples and discovered a reorganization of their communication following learning. Notably, this reorganization appeared specifically for CA1 superficial (CA1sup) sublayer neurons. Utilizing a generalized linear model decoder, we demonstrate the pre-existence of ACC-to-CA1sup communication, which is suppressed during new learning and subsequent sleep suggesting that ACC activity may reallocate the contribution of CA1sup neurons during memory acquisition and consolidation. Further supporting this notion, we found that optogenetic stimulations of the ACC preferentially suppressed CA1sup interneurons while activating a unique subset of CA1 interneurons. Overall, these findings highlight a possible role of the ACC in rebalancing CA1 neuronal populations' contribution to ripple contents surrounding learning.

Disclosures: A. Hall: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.07/II5

Topic: I.08. Learning and Memory

Support: NIH Grant R01MH119102
NIH Grant R21MH134016

Title: Anterior Cingulate Cortex to Median Raphe Circuit in Discrimination-Avoidance Associative Learning

Authors: *W. HUANG;
Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Effective adaptive behavior for survival depends on the brain's ability to form and update cue-action-outcome associations in response to environmental stimuli. The anterior cingulate cortex (ACC) has been implicated in these processes; however, its precise role in action monitoring and outcome evaluation remains incompletely understood. To address this, we developed a novel discrimination-avoidance task for mice, designed to temporally dissociate actions from outcomes. Our findings reveal that ACC neurons primarily encode post-action variables over extended periods, reflecting preceding actions rather than the outcomes or values of those actions. Notably, we identified two distinct subpopulations of ACC neurons: one encoding the *action state* (i.e., whether an action occurred) and the other encoding *action content* (i.e., which specific action was taken). Increased post-action ACC activity was associated with improved performance in subsequent trials, suggesting a role in sustaining action-relevant information to support future behavior. These results indicate that the ACC contributes to complex associative learning by maintaining extended representations that bridge cue, action,

and outcome associations. Ongoing experiments are aimed at establishing the causal role of the ACC and its projection pathways in learning, using optogenetic activation and inhibition to manipulate either ACC neurons directly or specific efferent pathways. In particular, recent evidence highlights the median raphe nucleus (MnR), especially its glutamatergic Vglut3-expressing neurons, as a key subcortical target of ACC projections. These MnR-Vglut3 neurons send ascending outputs to learning-related regions, predominantly targeting inhibitory interneurons and modulating circuit excitability and synchrony. Our current work seeks to elucidate how the ACC-MnR pathway contributes to top-down regulation in adaptive active avoidance learning, and to clarify how this cortical projection shapes broader brain-wide learning circuits.

Disclosures: W. Huang: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.08/II6

Topic: I.08. Learning and Memory

Support: STI 2030-Major Projects (2022ZD0207500 to J.Z.)

Title: Causal evidence for opposing roles of hippocampus and orbitofrontal cortex in associative memory organization

Authors: *H. LIN^{1,2}, J. ZHOU³;

¹Chinese Inst. for Brain Res., Beijing, China; ²Acad. for Advanced Interdisciplinary Studies, Peking Univ., Beijing, China; ³State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ. & Chinese Inst. for Brain Res., Beijing, China

Abstract: The ability to establish associations between environmental stimuli is fundamental for higher-order brain functions like state inference and generalization. Both the hippocampus and orbitofrontal cortex (OFC) are essential for organizing associative memory, with recent research highlighting their complementary roles: the hippocampus encode more specific associations, while the OFC facilitates generalization of similar associations. Despite this, their causal interdependence—particularly how dysfunction in one region impacts the other—remains poorly understood. Here, we trained head-restrained mice to learn four ‘odor-outcome’ sequence pairs composed of several task variables—the past and current odor cues, sequence structure of ‘cue-outcome’ arrangement, and the expected outcome—and performed calcium imaging in these mice throughout learning, combined with pharmacological lesions. Our results revealed that CA1 lesions significantly enhanced outcome prediction representation in the OFC, manifested as high generalization across sequences, epochs, and trials. In contrast, OFC lesions mildly impaired the generalization of long-delay sequences in the CA1, indicating an asymmetric interaction between

the two regions. These findings suggest that under normal conditions, a hierarchical regulatory mechanism may exist between the two regions: the CA1 provides bottom-up context-specific information to constrain excessive generalization of outcome-related associations in the OFC, while the OFC delivers top-down outcome prediction signals to promote generalization representation in the CA1. Taken together, these results suggest that the hippocampus and OFC work in a complementary manner to organize acquired associative structures, exerting opposing roles in each other's representation and balancing the interplay between discrimination and generalization in cognitive maps.

Disclosures: H. Lin: None. J. Zhou: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.09/II7

Topic: I.08. Learning and Memory

Support: RF1 Grant AG081767
McKnight Brain Research Foundation

Title: Increased mPFC-ivHC theta synchrony during correct task choice observed in young but not in old rats

Authors: *C. STERZINAR¹, S. V. SRIVATHSA², M. SPONSELLER³, V. M. GARZA³, E. R. CHURCH⁴, M. WARRIER³, S. L. COWEN⁵, C. A. BARNES⁶;

¹Univ. of Arizona, Chandler, AZ; ²Neurosci. GIDP, ³Univ. of Arizona, Tucson, AZ; ⁴Univ. of Arizona, Phoenix, AZ; ⁵Dept. of Psychology, ⁶Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ

Abstract: Amongst cognitive functions susceptible to age-related decline in mammals, spatial and working memory processes are notably affected. These processes rely on the hippocampus and medial prefrontal cortex (mPFC), which play a critical role in memory-guided navigation and decision making. Communication between these structures is thought to be facilitated via theta oscillations (6-12Hz) which occur in the hippocampus during locomotion and in the mPFC during periods of elevated working memory demand. Increased theta synchrony between the hippocampus and mPFC is thought to correlate with better performance on spatial working memory tasks. Little is known about how synchrony between these two regions is affected with age and its correlation with decline in spatial working memory function. We trained young (n=8) and old (n=8) male F344 rats on a spatial alternation task where we observed reduced performance of the old rats on the spatial working memory component of the task even after 21 sessions. Following acquisition of the spatial alternation task, rats were implanted with dual-bundle hyperdrives targeting the intermediate and ventral CA1 region of the hippocampus

(ivHC) and both the prelimbic (PL) and infralimbic (IL) regions of the mPFC. Robust theta activity was observed in the ivHC during locomotion in both aged and young rats with no differences in theta power between age groups. mPFC-ivHC theta synchrony was higher when young rats made the correct spatial choice compared to incorrect ones. In contrast, there was no correlation between task performance and theta synchrony observed in old rats. Interestingly, while theta coherence was observed across the entire dorso-ventral axis of the mPFC, there was greater synchrony between the ivHC and the ventral mPFC region (infralimbic) compared to the dorsal mPFC region (prelimbic) in both age groups. This suggests that during decision making at the choice point, different mPFC regions are differentially engaged with the ivHC. These results indicate that while mPFC-ivHC coherence is a strong predictor of accurate performance in young rats, it is an unreliable predictor of performance in aged rats. This implies that aged rats might rely less on hippocampal-prefrontal circuits compared to young rats to perform the spatial alternation task and instead use alternate brain pathways. Another possibility is that aged rats use oscillations of different frequencies to synchronize between these regions. In support of this, we observe oscillations in the mPFC and ivHC in the delta (2-6Hz) and gamma (30-80Hz) bands prior to the choice point, although the correlation of these oscillations to task variables is still to be determined.

Disclosures: C. Sterzinar: None. S.V. Srivathsa: None. M. Sponseller: None. V.M. Garza: None. E.R. Church: None. M. Warriar: None. S.L. Cowen: None. C.A. Barnes: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.10/II8

Topic: I.08. Learning and Memory

Support: RF1AG081767
McKnight Brain Research Funding

Title: Aged rats show reduced evoked medial PFC response to ventral hippocampus stimulation

Authors: *S. V. SRIVATHSA^{1,2,3}, A. VISHWANATH³, V. M. GARZA², S. L. COWEN^{3,2}, C. A. BARNES^{2,3};

²Evelyn F. McKnight Brain Inst., ³Dept. of Psychology, ¹Univ. of Arizona, Tucson, AZ

Abstract: Interactions between the hippocampus and prefrontal cortex are known to play a crucial role in spatial working memory processes which are known to be impaired in aging. These regions are connected via a monosynaptic, unidirectional projection from the CA1 layer of intermediate (iHC) and ventral (vHC) hippocampus to the mPFC. Damage or inhibition of this connection leads to impairments in spatial working memory tasks. However, little is understood about how monosynaptic iHC and vHC inputs differentially engage neural activity along the

dorso-ventral axis of the mPFC or how this is affected by aging. We delivered 25 individual biphasic electrical pulses (halfwidth: 0.5 ms) ranging in amplitude from 100-600 μ A with a 30 s interval between pulses. Pulses were delivered to CA1 in iHC and vHC in anesthetized male F344 young (10 months, n = 6) and old (24 months, n = 5) rats. We simultaneously recorded evoked neural activity along the dorsoventral length of the mPFC using Neuropixels 2.0 probes. These recordings were obtained from all 4 shanks spanning the prelimbic (PL) and infralimbic (IL) regions (areas 24b and 25) of the mPFC. This method allowed us to observe the gradient of responses to each stimulation throughout the mPFC. Upon stimulating either the iHC and vHC, we observed that the mPFC response was first observed in the infralimbic region followed by the prelimbic region in both young and old rats. Additionally, the magnitude of the evoked response to both iHC and vHC stimulation was greater in some infralimbic areas compared to the prelimbic regions in both age groups. These findings align with prior anatomical studies that found more ivHC synaptic terminals in the infralimbic region than prelimbic. Within the hippocampus, vHC stimulation evokes larger overall mPFC synaptic responses than iHC, in both age groups. These findings suggest that the strongest synaptic connections are from the vHC to the infralimbic region. With respect to age, the size of the evoked response in both mPFC regions was reduced in the old rats compared to the young. The weakening of synaptic input in old rats could be indicative of axonal pruning or a reduction of synaptic strength of the ivHC projections to the mPFC with age.

Disclosures: S.V. Srivathsa: None. A. Vishwanath: None. V.M. Garza: None. S.L. Cowen: None. C.A. Barnes: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.11/II9

Topic: I.08. Learning and Memory

Support: RF1 Grant AG081767
McKnight Brain Research Foundation

Title: Old rats continue to switch between allocentric and procedural strategies throughout spatial learning

Authors: *M. SPONSELLER¹, S. V. SRIVATHSA², S. L. COWEN³, C. A. BARNES⁴;
²Neurosci. GIDP, ³Dept. of Psychology, ⁴Evelyn F. McKnight Brain Inst., ¹Univ. of Arizona, Tucson, AZ

Abstract: Episodic memory deficits, such as spatial learning, are cognitive impairments that occur with aging in mammals. The Morris watermaze is a behavioral task used to assess spatial memory in rodents and their hippocampus-dependent navigation performance. The task requires

the animal to locate a hidden platform beneath the surface of the water from varying start locations utilizing visual cues from around the room to form an allocentric spatial map. Multiple previous studies have shown that aged rats are consistently impaired in navigating to the platform across days of learning when compared to young rats. It is unknown how differences in the strategy types of young and old rats on this task may lead to the observed deficits in aged rat performance. We trained young (6-9 mo, n=37) and old (19-22 mo, n=65) male Fischer 344 rats on the Morris watermaze for four consecutive days of training with six trials per day. Using an automated machine-learning classifier (Rtrack, Overall et al., 2020), we quantified the probability of eight different navigation strategies on every trial. These strategies were determined by the trajectory the rat took on a given trial and the proximity of the trajectory to the platform. We found significant differences in the use of strategies between the two age groups across learning of this task. Young rats increased their use of allocentric search strategies across learning, while decreasing their use of procedural (egocentric) and non-goal-oriented strategies. In contrast, old rats do not show a decrease in the use of procedural strategies across learning. The old rats also showed an increase in the use of allocentric strategies and learning, but they favored the less spatially efficient allocentric strategies compared to young rats. Entropy and first-order Markov transition analyses further revealed that individual young rats converged onto a restricted set of allocentric strategies by Day 4. Old rats, however, continued to switch between procedural and allocentric strategies (higher entropy). These results align with human literature that hypothesizes that aging shifts the balance of strategy selection from relying on hippocampus-dominant allocentric circuits to extra-hippocampal circuits involved in procedural strategies.

Disclosures: M. Sponseller: None. S.V. Srivathsa: None. S.L. Cowen: None. C.A. Barnes: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.12/II10

Topic: I.08. Learning and Memory

Support: McKnight Brain Research Foundation

Title: Arc mRNA expression pattern in CA1 hippocampal subregion reveals ensemble stability differences across age and cognition

Authors: *Y. CHEN¹, M. K. CHAWLA², M. A. ZEMPARÉ³, S. KHATTAB⁴, C. A. BARNES²;

¹Univ. of Arizona Grad. Interdisciplinary Program In Neurosci., Tucson, AZ; ²Evelyn F. McKnight Brain Inst., ³Neurosci. GIDP, ⁴Univ. of Arizona, Tucson, AZ

Abstract: Cognitive function alters with age, yet these age-related changes have varying effects across individuals. The neural circuit mechanisms underlying this variability remains poorly understood. To address this, we investigated the stability of hippocampal neural ensembles among individuals with differing spatial memory ability across the rodent lifespan. Our study focused on the CA1 subregion of the hippocampus, which receives topographically organized input from the entorhinal cortex. Specifically, distal CA1 receives projections from the lateral entorhinal cortex (LEC), proximal CA1 from the medial entorhinal cortex (MEC), and medial CA1 from both cortices. These distinct inputs result in functional segregation along the CA1 transverse axis. In this study, catFISH (cellular compartment analysis of temporal activity by fluorescence in situ hybridization) was used to map Arc mRNA expression in hippocampal neuronal populations at single-cell resolution. This allowed us to assess network stability by identifying cells activated during two separate behavior sessions. We obtained male Fischer-344 rats from three age groups (6, 15, and 23 months). In order to capture individual variability within each age group, rats were classified into high, average, and low performing groups based on their Morris watermaze performance. Rats were allowed to explore the same environment twice for 5 minutes each, separated by a 20-minutes rest period in their home cage. We hypothesize that both aging and cognitive status will be associated with differential ensemble stability in CA1. Previous ANOVA results from the middle CA1 revealed a significant age effect ($F[2, 81] = 7.103, p < 0.01$) within the high-performing group, with old rats exhibiting a higher proportion of double-labeled Arc-positive cells, suggesting greater network stability compared to other performance groups. Here we present data obtained from proximal and distal CA1. Within the high-performing group, ANOVA results showed a marginally significant effect of age in both proximal and distal CA1. Proximal CA1 of old high-performing rats, on the other hand, exhibited a higher proportion of double-labeled Arc-positive cells than did young and middle-aged rats. These region-specific results are particularly interesting because the proximal region receives the densest input from the MEC. The information content carried by these inputs is presumed to be primarily spatial, and the differences in network stability may contribute to the better performance of these high-performing old rats.

Disclosures: Y. Chen: None. M.K. Chawla: None. M.A. Zempare: None. S. Khattab: None. C.A. Barnes: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.13/II11

Topic: I.08. Learning and Memory

Support: R01 NS123424
R01 RF1AG081767
McKnight Brain Research Foundation

Title: Dorsal hippocampal neurons differentially respond to dimensions of time and length during a fine-motor behavior

Authors: *G. HOLGUIN¹, Z. HUESTIS², A. WHITE¹, Y. M. SURTCHEV¹, K. JORGENSEN¹, A. TAPIA¹, C. A. BARNES³, S. L. COWEN⁴;

¹Univ. of Arizona, Tucson, AZ; ²Univ. of Arizona, TUCSON, AZ; ³Evelyn F. McKnight Brain Inst., ⁴Dept. of Psychology, Univ. of Arizona, Tucson, AZ

Abstract: Neural activity in the hippocampus accurately encodes spatiotemporal information during navigation and spatial working memory behaviors, and this activity is believed to underlie the formation and retrieval of episodic memories. While hippocampal single-unit function is largely tied to spatial encoding and retrieval, evidence suggests that hippocampal representations, under the appropriate context and task, can flexibly encode other dimensions such as time and auditory frequency. The present study sought to determine if such representations can extend to ‘length pulled’ in a novel bi-manual string-pulling behavior (Jordan et. al., 2024) where reward was delivered only when a predetermined length of string was pulled.

Methods: Male (n=7) and female (n=3) Sprague-Dawley rats were trained on the string-pulling task that required animals to pull either a short (125cm) or long (250cm) length of string. Each pulling bout was followed by running on a circular two-meter track to retrieve food reward. Neuropixels recordings were acquired from dorsal hippocampal CA1 and CA3 (AP: 3.35 ML: 2.8 DV: -2.4 to -4.2). **Results:** Of the 1,444 putative pyramidal neurons, 19.6% responded to time only, 39.1% responded to length only, and 41.3% responded to both length and time. The observation that more cells responded to length relative to time suggests that hippocampal neurons preferentially mapped to the task-relevant dimension (length of string pulled). Animal behavior also indicated that rats monitored the length of string pulled. For instance, in randomized probe trials where the expected reward was omitted, a one-way ANOVA revealed a significant increase in pulling speed at the time expected reward ($p < 0.001$). Furthermore, a small subset of neurons displayed distinct activity patterns on probe trials that were precisely aligned to the expected but omitted reward. These findings are consistent with the idea that the hippocampus responds to task-relevant dimensions, such as pulled string ‘length’ in our task, while subsets of cells responded to length and time. This work provides novel insight into the extent to which the hippocampus flexibly represents meaningful dimensions beyond space and time.

Disclosures: G. Holguin: None. Z. Huestis: None. A. White: None. Y.M. Surtchev: None. K. Jorgensen: None. A. Tapia: None. C.A. Barnes: None. S.L. Cowen: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.14/II12

Topic: I.08. Learning and Memory

Support: NIH small instrumentation grant S10 OD025016
National Institute of Aging of the National Institutes of Health Training Fellowship T32AG082631-01
Arizona Department of Health Services (ADHS) AG003376
McKnight Brain Research Foundation
state of Arizona (ADHS Grant No. CTR057001)

Title: Microstructural Changes in Locus Coeruleus-Cortical Projections in Aged Bonnet Macaques are Independent of Myelin Loss

Authors: *L. DIECKHAUS¹, K. MCDERMOTT², V. SANDRIN², C. J. COMRIE¹, E. B. HUTCHINSON¹, C. A. BARNES³;

¹Biomed. Engin., ²Neurosci., ³Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ

Abstract: The locus coeruleus (LC) is a brainstem nucleus best known for being the primary site of noradrenaline production for the forebrain and is involved in the modulation and optimization of behavioral performance. The LC has many targets throughout the cortex, and ascending projections from the LC join the central tegmental tract (CTT), a well-defined white matter brainstem tract in the pons that terminates in the thalamus. Evidence indicates that the LC is one of the first brain regions to show pathological burden in Alzheimer's disease (AD), and AD patients exhibit structural alterations in the LC and its ascending projections. The extent to which changes occur in the LC and its projections in normal aging, however, is less clear. Analysis of LC-forebrain tractography has historically been difficult due to the small size of the LC as well as the abundance of crossing fibers in the brainstem. *Ex vivo* magnetic resonance imaging (MRI) at high resolution enables small tract visualization and measurement. Here, we utilize a cohort of 7 bonnet macaques, an excellent model of normative aging, and analyze the microstructure of the LC and its projections that join the CTT with respect to age. Within the LC, we found subtle changes in diffusion-based metrics in aging. In the CTT, we found alterations in diffusivity metrics such that aged animals exhibit lower fractional anisotropy (FA) and axial diffusivity (AD) values. There were no significant age-related associations with volume of the tract nor metrics of myelin content. This suggests that the LC-CTT does not experience loss of myelin or axons during the normal aging processes in nonhuman primates. While we cannot directly confirm this, the lower FA and AD values are consistent with inflammation-related changes that occur during aging, which can impact the microstructural environment.

Disclosures: L. Dieckhaus: None. K. McDermott: None. V. Sandrin: None. C.J. Comrie: None. E.B. Hutchinson: None. C.A. Barnes: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.15/II13

Topic: I.08. Learning and Memory

Title: Relationship between fornix diffusion tensor imaging and cognitive function in cynomolgus monkeys

Authors: *R. NISHIKATA¹, Y. HORIMOTO², K. HAYASHIDA²;

¹SHIN NIPPON BIOMEDICAL LABORATORIES, kagoshimashi, Japan; ²Shin Nippon Biomed. Laboratories, Ltd., Kagoshima, Japan

Abstract: The fornix, a key hippocampal-hypothalamic pathway, is vital for memory and spatial cognition. Clinical studies using diffusion tensor imaging (DTI) have shown that higher fornix fractional anisotropy, which reflects tract density and serves as a marker for tract volume, is associated with better cognitive performance in older adults. This study investigated whether age and fornix volume relate to cognitive function in cynomolgus monkeys. We examined the relationship between fornix volume, age, and cognitive function in 24 cynomolgus monkeys (11 males, 13 females, aged 9–23 years). Learning and memory function was assessed using a finger maze task, while fornix volume was measured via diffusion tensor tractography (DTT) before and after the task. Our results revealed a significant positive correlation between fornix volume and learning speed, with a positive correlational trend observed for memory performance. Fornix volume increased during the training period of the finger maze task, with older animals exhibiting a greater change in volume by the end of the training. These findings suggest that the fornix plays a crucial role in learning and memory in cynomolgus monkeys, mirroring human findings. The observed task-related increase in fornix volume, which was particularly pronounced in older animals, warrants further investigation into its underlying mechanisms and implications on neuroplasticity. This study enhances our understanding of cognitive impairment mechanisms and underscores the potential of DTI/DTT-based fornix measurements as a cognitive biomarker.

Disclosures: R. Nishikata: None. Y. Horimoto: None. K. hayashida: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.16/II14

Topic: I.08. Learning and Memory

Title: Gamma-ray-induced Suppression of Neurogenesis Disrupts Cognitive Discrimination in Non-human Primates

Authors: *M. KIM^{1,2};

¹Korea Res. Inst. of Biosci. and Biotech., Cheongju-si, Korea, Republic of; ²Bio and Brain Engin., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The dentate gyrus of the mammalian hippocampus continues to generate new neurons throughout adulthood. These adult-born neurons become functionally integrated into existing circuits and are believed to contribute to learning and memory, particularly during their maturation phase when they exhibit heightened synaptic plasticity. While adult hippocampal neurogenesis has been well-documented in rodents, recent studies have extended these findings to other mammalian species, including non-human primates. In this study, we demonstrate that gamma ray irradiation, which reduces the population of adult-born neurons, impairs cognitive performance in a task requiring fine object discrimination between two highly similar shapes. Following irradiation, monkeys with reduced levels of adult hippocampal neurogenesis showed significant deficits in object discrimination, suggesting impaired pattern separation. We also used diffusion tensor imaging to monitor brain structural changes over time. While overall FA decreased, we observed a localized FA increase in the hippocampus, potentially reflecting reduced neurogenesis and altered microstructural integrity in this region. Together, these results indicate that decreased adult hippocampal neurogenesis in non-human primates impairs pattern separation and is associated with structural changes in the brain, underscoring the functional significance of adult-born neurons in cognitive processing.

Disclosures: M. Kim: A. Employment/Salary (full or part-time): KRIBB.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.17/JJ1

Topic: I.04. Executive Functions

Support: MH R01136013

Title: Inhibitory neuronal subpopulations in the hippocampus in rhesus monkeys

Authors: *V. VERMA¹, B. ZIKOPOULOS², H. BARBAS³;

¹Dept. of Hlth. Sci., ²Boston Univ., Boston, MA; ³Hlth. Sciences, and Anat. and Neurobio., Boston Univ., Brookline, MA

Abstract: The hippocampal formation (HF), which includes the hippocampus (HPC), dentate gyrus (DG), subiculum, and entorhinal cortex (EC) in the medial temporal lobe (MTL), is involved in mnemonic processes. Briefly, the flow of information in the HF is largely unidirectional, initiated from layer III of the EC, which projects through the perforant pathway (PP) to the DG, and continues through the mossy fibers to CA3. The CA3 projects via the Schaffer collateral pathway to CA1, which subsequently projects to the subiculum and the deep layers of EC. The complex processing in the HF is fine-tuned by functionally and neurochemically distinct types of inhibitory neurons labeled for calretinin (CR), calbindin (CB), and parvalbumin (PV), which account for most of the inhibitory neuronal population in the

primate HPC. Here, we characterized the inhibitory populations in each layer and region of the HPC of the rhesus macaque, which included CA3, CA2, and CA1. In the HPC, the most superficial layer is the Lacunosum/Moleculare (LM) followed by the Stratum Radiatum (St Rad), the Stratum Pyramidale (St Pyr), the Stratum Oriens (St Ori), and the Stratum Alveus (St Alv), which is the most deep layer. We used stereological methods to estimate the density of inhibitory neurons labelled for CR, CB, PV, and GABA in the HPC. Additionally, we analyzed the density of Reelin (RLN) positive neurons, which are expressed early in development, and persist in some structures, including the HF. Our results showed an uneven distribution of inhibitory neurons throughout the hippocampal regions and layers. There was a trend of high number of GABA-positive neurons in the deep layers (St Alv-St Ori) compared to the superficial layers (LM-St Pyr) of the HPC. Some HPC GABAergic neurons were positive for RLN, with the highest density seen in the LM. We found that CR neurons had the highest density in HPC distributed in the LM and at the border of LM and St Rad, followed by CB neurons, which were scattered throughout St Rad but were found in higher number in the St Pyr and at the border between St Pyr and St Ori. PV neurons were the least dense, and were distributed in the St Ori and at the border between St Pyr and St Ori. CR neurons were most densely distributed in CA1, while CB and PV neurons were most dense in CA3. The inhibitory profile of these layers may help elucidate their potential impact on both the intrinsic and extrinsic hippocampal circuits. The HPC is affected in disorders that include autism and schizophrenia, often exhibiting atrophy and neuronal loss. These findings provide a foundation for future comparisons with information from neurotypical human brains and various neuropathological conditions.

Disclosures: V. Verma: None. B. Zikopoulos: None. H. Barbas: None.

Poster

PSTR044: Learning and Memory Operations in Cortical and Hippocampal Networks: Cellular, Network, and Behavioral Studies

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR044.18/JJ2

Topic: I.08. Learning and Memory

Title: Voluntary and Reflexive Eye Behaviors Track Recognition Memory Signals in Posterior Parietal Cortex of a Single Macaque

Authors: S. ZHANG¹, *J. LIU², J. CAI³, C. XUE⁴, Z. JIN⁵, M. CAO⁶;

¹Univ. of Iowa, Iowa City, IA; ²East China Normal Univ., Shanghai, China; ³King's Col. London, London, United Kingdom; ⁴Univ. of Califor, San Francisco, CA; ⁵Duke Kunshan Univ., Kunshan, China; ⁶Johns Hopkins Univ., Baltimore, MD

Abstract: The posterior parietal cortex (PPC) is thought to integrate attention and memory processes. However, how voluntary eye movements and involuntary pupil responses reflect recognition memory signals in PPC remains unclear. We recorded single-unit activity from the PPC of a male rhesus macaque (*Macaca mulatta*, “Mars”) during a three-alternative forced-

choice (3AFC) delay-matching-to-sample (DMTS) task. In each retrieval trial, one previously seen image (target) and two novel images were displayed, and the monkey indicated the familiar stimulus while voluntary ocular behaviors (fixations, saccades) and reflexive pupil responses were tracked throughout task encoding and retrieval. PPC firing rates positively correlated with fixation and saccade behavior ($p < 0.05$) and negatively with blink rate ($p < 0.05$), in both encoding and retrieval phases. Notably, during retrieval, saccade-related PPC activity was significantly stronger on correct recognition trials compared to incorrect trials, suggesting that coordinated gaze shifts are more effectively aligned with memory-guided neural responses during successful recognition. Pupil diameter was standardized within each fixation during the decision-making period and divided into eight proportional bins (each covering 12.5% of the pupil size range). Descriptively, PPC firing rates appeared highest in an early bin (12.5-25%) and lowest in a mid-to-late bin (62.5-75%), suggesting a potential sensitivity to early arousal. PPC neuron responses reflected both novelty and familiarity across different timescales. During the retrieval phase, PPC neurons fired more strongly to novel stimuli (foils) than to familiar targets ($p < 0.001$), indicating a novelty preference. At the loop level, across 25 repeated exposures of the same images, we observed that the number of responsive PPC neurons increased with each repetition, consistent with growing familiarity over time. Together, our findings demonstrate that recognition memory retrieval engages distinct voluntary (oculomotor) and involuntary (autonomic) components, each associated with distinct patterns of PPC activity. By distinguishing attention-driven gaze orienting from reflexive pupil-linked arousal, this study provides insight into how PPC bridges attention and memory, highlighting the interplay of cognitive and autonomic processes in recognition memory.

Disclosures: S. zhang: None. J. Liu: None. J. cai: None. C. Xue: None. Z. Jin: None. M. Cao: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.01/JJ3

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (JP18H05213, JP23H05476)
JSPS KAKENHI (20H03554, 23H02785)
CREST JPMJCR23N2
AMED PRIME 23gm6510028h0001
The Uehara Memorial Foundation
The Naito Foundation

Title: Cholinergic neurons modulate brain-state-dependent oscillatory dynamics of synaptic transmission efficacy

Authors: *H. WANG^{1,2,3}, M. NOMOTO^{1,2,3,4}, K. YAMADA-NOMOTO^{1,2,3}, E. MURAYAMA^{1,2,3}, S. HAMADA⁵, T. OHTSUKA⁵, K. INOKUCHI^{1,2,3};

¹Grad. Sch. of Med. and Pharmaceut. Sci., Univ. of Toyama, Toyama, Japan; ²Res. Ctr. for Idling Brain Science, Univ. of Toyama, Toyama, Japan; ³CREST, Japan Sci. and Technol. Agency (JST), Univ. of Toyama, Toyama, Japan; ⁴Japan Agency for Med. Res. and Develop. (AMED), Tokyo, Japan, Tokyo, Japan; ⁵Fac. of Medicine, Univ. of Yamanashi, Chuo, Japan

Abstract: Sleep has been reported not only to consolidate memories but also to actively process information. It has been demonstrated that synaptic plasticity is dynamically modulated across the sleep-wake cycles. However, how the hippocampus processes memories during sleep remains largely unknown. We hypothesized that the oscillatory dynamics of hippocampal synaptic transmission across sleep-wake cycles play an important role in information processing. To test this, we first established an optophysiological and electrophysiological recording system for simultaneous calcium imaging and LFP recording from the hippocampal CA1 subregion with customized optrode combined with fiber photometry and electrode. We found that in the hippocampus, synaptic transmission efficacy between CA3-contralateral CA1 oscillated periodically with the wake-sleep cycle and was significantly enhanced during sleep compared to wakefulness. To further elucidate the mechanisms underlying the modulation of these oscillatory dynamics, we pharmacologically inhibited the cholinergic neural circuit by intraperitoneal injection of atropine, a muscarinic acetylcholine receptor antagonist, and observed a significant increase of synaptic transmission during wakefulness, indicating a disruption of these oscillatory dynamics. In addition, we chemogenetically inhibited hippocampal parvalbumin-positive (PV+) interneurons and found an increase of CA3-contralateral CA1 synaptic transmission efficacy in both wakefulness and sleep, with the oscillatory dynamics intact. These results suggested that cholinergic neurons modulate the oscillatory dynamics of synaptic transmission efficacy. To understand the functional role of our finding in information processing during sleep, we established a behavioral paradigm in which water-restricted mice were first trained to prefer a short path over long path for obtaining sucrose reward, then trained to avoid the short path by delivering air puffs. We found that atropine-injected group showed impaired avoidance memory, compared to saline-injected group, at 6 h test, suggesting that cholinergic neuronal activities are involved in memory update during sleep. Currently, we are planning to conduct optogenetic manipulation of cholinergic neuron terminals in hippocampal CA1 to further investigate the regulatory role of cholinergic neurons in behavioral output. Taken together, our findings expand the understanding of the importance of hippocampal information processing mode transitions between wakefulness and sleep.

Disclosures: H. Wang: None. M. Nomoto: None. K. Yamada-Nomoto: None. E. Murayama: None. S. Hamada: None. T. Ohtsuka: None. K. Inokuchi: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.02/JJ4

Topic: I.08. Learning and Memory

Support: NIH Grant R01MH124047
NIH Grant R01NS131728
NIH Grant RF1AG080818

Title: Functional characteristics of dCA1 neurons in spatial memory encoding

Authors: *Y. XIN¹, D. S. PETERKA², A. LOSONCZY³;
²Zuckerman Inst., ¹Columbia Univ., New York, NY; ³Neurosci., Columbia Univ., Westport, CT

Abstract: Flexibly encoding and memorizing the external environment is vital in cognitive function. The hippocampal region has long been acknowledged as a key brain region involved in context recognition and memory formation. Although extensive research has been conducted to comprehend the functions of the hippocampal circuit, the precise mechanisms by which this distinct neural circuit is capable of efficiently and reliably encoding memory remain largely unclear. In this study, we trained head-fixed mice to navigate virtual reality environments in search of water rewards at designated locations and conducted in vivo two-photon imaging to simultaneously record dCA1 population activity. By monitoring the spatial information encoding of the same population of neurons over a week, we identified three distinct functional neuronal types based on their place field formation propensity, place field (PF) stability, and ability to encode reward locations. Collectively, these functional groups allow the CA1 circuit to be flexible, efficient, and robust in encoding environmental information. Based on their functional property, we propose that the three functional groups may exhibit distinct abilities to form new place fields. We assessed these assumptions using the two-photon optical stimulation method to manually induce new place fields and compare new PF formation success rates between these functional groups. Consistent with our anticipation, there is a significant difference in the new PF induction success rate among the three groups. This disparity may be attributed to their distinct roles in encoding different aspects of memory. In summary, we identified different functional groups in the dCA1 region related to multi-context spatial memory task. We verified our assumptions regarding the internal characteristics of spatial information encoding preferences for these functional groups using optical manipulation methods. We proposed that the collaborative response of these functional groups can facilitate flexible and robust encoding of changing environments. Our findings will enhance our understanding of how the hippocampal circuit flexibly encodes memory and lays the basis for cognitive processes.

Disclosures: Y. Xin: None. D.S. Peterka: None. A. Losonczy: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.03/JJ5

Topic: I.08. Learning and Memory

Support: NS113557
MH103325

Title: Goal overrepresentation in hippocampal replay emerges from enhanced local excitability and attractor dynamics

Authors: *C. S. MALLORY¹, J. WIDLOSKI², D. J. FOSTER³;

¹Foster Lab/Uc Berkeley, Kensington, CA; ²Neurosci., UC Berkeley, Berkeley, CA;

³Psychology, Univ. of California, Berkeley, Berkeley, CA

Abstract: We previously showed that hippocampal replay can emerge from a recurrent network with continuous attractor dynamics and neuronal fatigue, explaining phenomena such as past-avoidance and replay self-avoidance (Mallory, Widloski & Foster, 2025). However, this model did not account for the goal-directed nature of replay—its tendency to overrepresent and terminate at remembered goal locations (Pfeiffer & Foster, 2013; Widloski & Foster, 2022). Here we provide evidence that goal overrepresentation emerges from altered excitability and attractor dynamics at the goal. In a spatial memory task where animals received identical rewards either at a consistent, learnable location (goal well) or at unpredictable locations (random wells), distinct patterns of hippocampal activity emerged. At the goal well, population burst events (PBEs) and sharp-wave ripples (SWRs) occurred at twice the rate observed at random wells, accompanied by elevated excitatory cell firing rates. Replays at the goal were slower, shorter, more locally anchored, and less avoidant of previously traversed or reactivated paths. Conversely, PBEs at random wells disproportionately represented the goal location, indicating a non-local overrepresentation. We hypothesized that the reduced replay propagation and diminished past-avoidance observed at goal locations reflect an attenuation of neuronal fatigue among goal-coding cells. In our network model, decreasing spike frequency adaptation at the goal well replicated these experimentally observed replay characteristics. These findings suggest that goal locations modulate hippocampal dynamics by creating zones of heightened excitability and reduced neuronal fatigue. When the animal is at the goal, this modulation resists replay propagation, thereby anchoring local reactivations. When the animal is situated elsewhere, enhanced excitability and reduced fatigue of goal-coding cells account for goal overrepresentation in reactivation events and the tendency of replays to terminate at these sites. Together, these results demonstrate how local changes in neuronal excitability at goal locations can influence the global patterns of hippocampal replay, offering a mechanistic explanation for goal-directed memory consolidation processes.

Disclosures: C.S. Mallory: None. J. Widloski: None. D.J. Foster: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.04/JJ6

Topic: I.08. Learning and Memory

Support: NIH Grant MH134515

Title: Connectivity profile of Kirrel3+ GABAergic neurons revealed by serial block-face scanning electron microscopy

Authors: *F. YE¹, K.-Y. KIM², T. BANDIATMAKUR¹, M. H. ELLISMAN³, M. E. WILLIAMS¹;

¹Univ. of Utah, Salt Lake City, UT; ²Univ. of California San Diego, La Jolla, CA, ; ³Sch. of Med., La Jolla, CA.

Abstract: Just as an efficient city relies on well-designed roads—where their size and connection points determine traffic flow—neurons depend on their synapse target, size, and dendritic location to ensure precise information transfer. While we generally understand these features well in primary neurons, they remain less characterized in GABAergic neurons due to their high diversity and sparse distribution. Our previous study identified the cell adhesion molecule Kirrel3 as a marker for a distinct subset of GABAergic neurons. Activating Kirrel3+ GABA neurons, but not parvalbumin(PV) neurons, significantly impairs memory discrimination. Moreover, both Kirrel3 and PV neurons activation inhibit CA3 neuron activity, but Kirrel3 GABA neurons inhibit CA3 activity to a significantly greater extent. Next, we sought to investigate how Kirrel3+ GABA neurons have such strong control over CA3 activity. We examined their synaptic connectivity at the light and electron microscope (EM) levels and compared the connectivity patterns of Kirrel3 GABA neurons to other types of GABA neurons in area CA3. Here, we present this new data in which we developed and used new intersectional tools to specifically label Kirrel3-GABA neurons and their synapses by light microscopy (using synaptophysin-GFP) and electron microscopy (using mitochondria-targeted APEX2). Together, these findings advance our understanding of the GABAergic connectivity profile in the hippocampus.

Disclosures: F. Ye: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.05/JJ7

Topic: I.08. Learning and Memory

Support: R21NS113024

Title: Mesoscale Functional Architecture of the Human Hippocampus During Memory Recognition

Authors: *W. HUANG, J. PARVIZI;
Stanford Univ. Sch. of Med., Stanford, CA

Abstract: The hippocampus (HPC) plays an important role in memory recognition, characterized by distinct electrophysiological signatures at the mesoscale level such as low-frequency activity (LFA) encompassing theta band, high-frequency activity (HFA) encompassing high-gamma, and ripple events. However, it remains unknown how these activities are generated by different subpopulation of neurons or distinct HPC subregions. In this study, we analyzed data from 26 patients with intracranial electroencephalography (iEEG, 187 HPC sites, 94 sites in the left hemisphere, median value is 6 sites across patients) while performing a verbal old-new memory recognition task for abstract and concrete words presented minutes or a day before. Combining data from immediate and delayed recognition tests, and measuring changes in the aperiodic exponent during recognition trials, we identified three groups of recording sites: Those showing an increase in the aperiodic exponent ($n = 79$ electrodes from 18 patients) with significantly higher HFA power and ripple rates for hit trials compared to miss, correct rejection, and false alarm trials during both post-stimulus onset and pre-response periods. These sites also showed increased LFA power during the post-onset period but a decrease during the pre-response period for hit trials compared to other conditions. In contrast, electrodes with a decrease in exponent ($n = 13$ electrodes from 9 patients) showed no significant memory-related differences; however, they did exhibit a significant increase in ripple rate during the pre-response period regardless of memory condition. Electrodes with no significant change in exponent ($n = 95$ electrodes from 23 patients) showed partial memory-related effects across specific conditions, reflected in LFA power and ripple rates but not in HFA power. Anatomically, the three electrode groups were not restricted to specific hippocampal subregions but were instead distributed in a mosaic-like pattern throughout the hippocampus. Our findings offer new insights into the mesoscale functional organization of the human hippocampus during memory recognition, indicating that distinct neural populations within the hippocampus play specialized roles while being interwoven and unevenly distributed across its structure.

Disclosures: W. Huang: None. J. Parvizi: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.06/JJ8

Topic: I.08. Learning and Memory

Support: University of Michigan Innovation Partnerships

Title: We salute you: A novel spatial learning and memory test for mice

Authors: *K. STANGIS¹, J. ZHANG², G. G. MURPHY³;

¹Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI; ²Univ. of Michigan Neurosci. Grad. Program, Ann Arbor, MI; ³MNI/MIP, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Mouse models are widely used for the purpose of biomedical research and serve as a vital tool for the study of neurological and psychiatric disorders. The creation of the first transgenic knock-out mouse in 1987 coincides with a rapid rise in the reported use of mouse models in the published biomedical literature. The cognitive function of rodent research models can be assessed by utilizing a variety of specialized behavioral tasks which target specific facets of attention, decision making, learning, and memory. One of the most cited assays used to evaluate learning and memory in rodents is the Morris Water Maze (MWM). This task was originally designed to assess spatial learning and memory in rats. The Barnes maze is an additional assay which is used to examine spatial learning and memory and was similarly initially developed for use with rats. As with many other widely utilized behavioral tasks, these tasks have not been greatly modified to be ethologically relevant to mice. Rats are semiaquatic animals which swim readily and make vertical burrows in the wild. While mice are capable of swimming under duress, they are terrestrial animals and do not make vertical burrows. Given these distinct differences in natural rat and mouse behavior, there is a need to develop ethologically relevant behavioral tasks for mice. We have developed a novel maze, referred to as “The Colosseum Maze”, to evaluate spatial learning and memory in mice specifically. This maze is designed to appeal to the instinctive behavior of mice to seek shelter in small holes above the ground. The escape box entrance is readily located and entered by 3-month-old male and female wildtype C57BL/6NTac mice. Escape latencies became asymptotically low within 7 training trials. No external motivation such as aversive noises, bright overhead lighting, or food deprivation was utilized to prompt the animals to seek the escape box, mitigating potential confounding sources of stress to the animals. Additional testing with cohorts of C57BL/6NJ, 129SvEv, C3H “Sighted”, and C57BL/6NTac x C3H “Sighted” F1 hybrid mice is currently under way. Additional efforts are ongoing to validate the apparatus with a mouse model of Alzheimer’s disease, which is well-documented to exhibit deficits in spatial learning and memory as assessed by the MWM.

Disclosures: K. Stangis: None. J. Zhang: None. G.G. Murphy: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.07/JJ9

Topic: I.08. Learning and Memory

Support: NIMH R01 grant 5R01MH120135, JY
Whitehall Foundation 20190851, JY

Title: Hippocampal awake sharp-wave ripples selectively bind spatial and reward information across the longitudinal axis

Authors: *K. FUKUMASU¹, J. YAMAMOTO^{1,2,3};

¹Psychiatry, ²Neurosci., ³Peter O'Donnell Jr. Brain Inst., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Memorizing reward locations is crucial for survival. To achieve this, animals must associate their spatial memories of the environment with reward-related experiences. However, how this association is established in the nervous system remains unclear. One candidate region for this process is the hippocampus (HPC). The dorsal HPC (dHPC) is specialized for spatial representation through abundant spatially tuned cells, while the ventral HPC (vHPC) encodes valence-related information via strong connectivity with the amygdala. Synchronous firing events across the HPC, known as sharp-wave ripples (SWRs), also play an essential role in learning and memory. We therefore investigated how SWRs affect ongoing interactions between dHPC and vHPC, and how these effects contribute to space-reward association. To address this, we simultaneously recorded spiking activities of up to 100-300 cells from dHPC and vHPC in freely moving mice using high-density silicon probes (Neuropixels). During recordings, animals were required to run toward the correct side (left or right) in a T-maze, while the correct side flipped every ten trials. The goal context was kept identical regardless of the flip, ensuring that the animals received the same sensory cues during reward consumption. Thus, they tried to maximize their reward by recognizing the current configuration based solely on spatial memories. By analyzing detected SWRs, we found that approximately 20% of cells exhibited dynamic responses to SWRs in ongoing activity during the task. While they showed gradually shifting firing rates over time, those directions were suddenly inverted from increase to decrease or vice versa at SWR onset. Notably, this post-SWR effect persisted for at least 10 seconds. As with firing rates, activity correlation of cell pairs also exhibited monotonic strengthening or weakening over time, with the direction abruptly reversed at SWRs. Specifically, after SWRs, cell pairs spanning dHPC and vHPC became increasingly correlated, whereas other cell pairs became progressively decorrelated. As expected, distribution of spatially tuned cells was biased toward dHPC, whereas activities of vHPC cells were focused on reward consumption. Presumably due to this, we also observed gradual reinforcement of correlation following SWRs between spatially tuned and reward tuned cells. Moreover, these responses of neuronal activity correlation to SWRs were predictable based on their activity patterns within SWRs. Taken together, these findings indicate that SWRs trigger memory processing for space-reward association across dHPC and vHPC, which may facilitate memorizing reward locations.

Disclosures: K. Fukumasu: None. J. Yamamoto: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.08/JJ10

Topic: I.08. Learning and Memory

Title: Neural correlates of memory strength dynamics in the primate hippocampus

Authors: *A. PICCATO¹, M. G. POTTA², G. M. STINE³, J. GABEL⁴, M. JAZAYERI⁵;

¹Brain and Cognitive Sci., ³Neurosci., ⁴McGovern Inst. for Brain Res., ²MIT, Cambridge, MA;

⁵Brain and Cognitive Sci., Massachusetts Inst. of Technol. Dept. of Brain and Cognitive Sci., Cambridge, MA

Abstract: A signature feature of long-term memory is its time- and experience-dependent strength. Memory strength directly impacts behavior: we recall recent and repeated experiences faster and more accurately than infrequent and remote ones. However, the neural and computational principles that link memory strength to accuracy and reaction time are not known. We designed a visuo-spatial association task that provides a window into memory strength dynamics through parametric control of the recency and repetition of prior experiences. Non-human primate subjects trained on the task acquire and retrieve visuo-spatial associations over tens of trials, allowing us to track memory strength dynamics for multiple novel associations within a single behavioral session. We find that both recency and repetition independently influence behavior, leading to more accurate choices and faster reaction times. To model this, we constructed a latent variable framework in which memory strength increases with exposure and decays exponentially over time. Incorporating this latent memory strength as the drift rate in a drift-diffusion model enables us to explain both choice accuracy and reaction time in terms of an underlying memory strength variable. Previous work has identified the hippocampus as a critical region for the formation of long-term associative memories. We recorded the activity of hundreds of neurons in the hippocampus of a trained macaque performing our task, aiming to identify a neural correlate of behavioral memory strength. We first characterized how the hippocampus encodes image-location associations and found that it does so in a highly conjunctive manner. We then examined how the structure of neural activity varies with memory strength as inferred by our model. We find that higher memory strength is associated with increased representational stability across trials for the same image-location association. Specifically, neural activity on high-memory-strength trials is more reliable, as reflected in both higher across-trial correlation and a smaller angle between population vectors compared to low-memory-strength trials. This progressive stabilization of the memory in the hippocampus may underlie the observed improvements in retrieval accuracy and speed.

Disclosures: A. Piccato: None. M.G. Potta: None. G.M. Stine: None. J. Gabel: None. M. Jazayeri: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.09/JJ11

Topic: I.08. Learning and Memory

Support: DP2 AG071918-01
Howard Hughes Medical Institute

Title: Hippocampal representation of memory contents in food-caching birds

Authors: *X. LI¹, S. HALE¹, D. ARONOV^{1,2};

¹Columbia Univ., New York City, NY; ²Howard Hughes Med. Inst. at Columbia Univ., New York City, NY

Abstract: Episodic memory is rich and multimodal, containing information about the “what,” “where,” and “when” of an event. It is therefore important to understand how neural activity binds these types of information. Food-caching birds like chickadees instinctively hide food across scattered sites and remember not only the locations, but also the contents of their caches. Their behavior thus combines at least the “where” and “what” components of memory. Memory for caches depends on the hippocampus, providing an ideal model for investigating how hippocampal activity integrates these components.

In our experiments, chickadees cached food in a laboratory arena containing 84 concealed cache sites. We provided chickadees with two types of food: their all-time favorite—pieces of peanut—and the less preferred chunks of coconut pulp. The latter were dyed with food coloring to allow automatic detection of what food birds were carrying or caching. We used silicon probes to record in the chickadee hippocampus. We analyzed moments when birds cached or retrieved food, as well as moments when they opened cache sites to “check” the contents without retrieving.

As in previous work, we found that the majority of neurons showed significant enhancement or suppression in their firing rate during these events. Of these cells, a large fraction had different responses depending on whether the bird was interacting with a peanut, coconut, or an empty site. The strongest difference between responses to different foods occurred after the offsets of caches—when a new memory is expected to form. In our preliminary data, peanut-preferring neurons were more numerous, suggesting that hippocampal activity was more devoted to the more valuable items. However, coconut-preferring neurons were also present in the data, demonstrating that not only the value, but the content itself might also be represented. Notably, most of the food-preferring cells were also place cells, suggesting that the “what” and “where” components of experiments are mixed in the activity of individual neurons.

Our work so far demonstrates an experimental paradigm in food-caching chickadees for studying how different components of memories are combined in neural activity. We are further exploring how the memory content representations we found here relate to the recently discovered “barcodes” that assign unique labels to different episodic memories in these birds.

Disclosures: X. Li: None. S. Hale: None. D. Aronov: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.10/JJ12

Topic: I.08. Learning and Memory

Support: NIH Grant 5R00MH119320

Title: Examining overlap in PL-VH projecting neuronal ensembles linked to fear or safety cues

Authors: *V. CASTRO¹, S. PRABHU², S. FRANCISCO², H. C. MEYER³;

¹Boston University, Brighton, MA; ³Psychological and Brain Sci., ²Boston Univ., Boston, MA

Abstract: Fear learning is adaptive, but when impaired it can be a hallmark of anxiety disorders. A form of fear regulation is safety learning, where the learned signal resembles the absence of a threat. Previous research has suggested that projections from the ventral hippocampus (VH) to the prelimbic cortex (PL) are involved in safety learning, through their role in inhibiting threat responses. However, it is unknown how this is carried out at the level of neuronal ensembles. This study aims to uncover the extent to which fear and safety memories are neurally linked, and if this differs across age. Male and female mice underwent stereotaxic surgery, where a doxycycline (DOX)-inducible cFos-tTa and cre-dependent TRE-DIO-eYFP virus cocktail was bilaterally infused into the VH and a cre-expressing retrograde-tdtomato virus was infused bilaterally into the PL. Following recovery, adolescent (PND 35-36) and adult mice (PND 70-75), underwent discriminative conditioning, where they learned to discriminate between a fear tone paired with a shock and an unpaired safety tone. Our results show that both, adults and adolescents learned discrimination between the two tones across four days. Mice were then taken off the DOX diet and 48 hours later, underwent a safety memory tagging session. Immediately after, mice were placed back on the DOX diet to close the tagging window. 24 hours later, mice underwent a second tagging session, with separate mice exposed to safety, fear, or neutral cues. During tagging sessions one and two, mice maintained high freezing for fear and lower freezing for safety, indicating sustained memory of cue salience. Brains were collected 90 minutes after the second tagging session and the VH was processed for cFos+ cells and previously tagged eYFP+ safety cells. Preliminary histological data suggests that there is less overlap in cFos+ and eYFP+ cells between tagging session one and two in adolescents compared to adults, possibly suggesting neuronal drift, particularly in adolescents who exhibit high neural plasticity. Overall, the data has the potential to inform the field on the neurobiological correlates underlying fear processing and regulation.

Disclosures: V. Castro: None. S. Prabhu: None. S. Francisco: None. H.C. Meyer: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.11/JJ13

Topic: I.08. Learning and Memory

Support: NIH Grant 1DP2
AFOSR
HHMI

Title: Dendrite-targeting OLM interneurons regulate the formation of experience-dependent CA1 place cell representations.

Authors: *E. P. CAMPBELL¹, L. MARTIN², J. C. MAGEE⁴, C. GRIENBERGER³;
¹HHMI / BCM, HOUSTON, TX; ²Biol., ³Dept. of Biol., Brandeis Univ., Waltham, MA;
⁴Neurosci., HHMI, Houston, TX

Abstract: Spatial learning requires the experience-dependent development of place cell representations in hippocampal area CA1. Previous results demonstrate that behavioral timescale synaptic plasticity (BTSP) has a fundamental role in novel place cell formation and shaping of CA1 representations. BTSP is initiated by dendritic Ca²⁺ plateau potentials triggered in the distal tuft region of CA1 pyramidal neurons. Our working model proposes that these plateau potentials result from the convergence of a target signal (known to be provided by excitatory input from the entorhinal cortex) and an inhibitory feedback signal reflecting the current state of the CA1 representation. However, the cellular source of this inhibitory feedback involved in BTSP has not yet been identified. A strong candidate neuronal subtype are the oriens lacunosum-moleculare (OLM) interneurons, which receive excitatory input from the local CA1 population and form synapses onto CA1 pyramidal neuron tuft dendrites.

Here, we used *in vivo* two-photon somatic and axonal calcium imaging to record the activity of somatostatin (SST)-expressing OLM interneurons in mice exploring a novel linear track for the first time. After correcting for the animals' dwell time with respect to space, we found that OLM activity aligns well with the inhibitory feedback predicted by our BTSP model. Thus, their activity increased as a function of learning, with a higher relative activity increase around the reward site.

We found that a subset of OLM interneurons that express the nicotinic receptor alpha 2 subunit (Chrna2 α) exhibits activity comparable to the larger SST-expressing OLM interneuron population, thus providing highly specific genetic access to the circuit elements mediating inhibitory feedback in CA1. Optogenetic activation of Chrna2 α -expressing OLM interneurons significantly reduced the frequency of BTSP events and Ca²⁺ events classified by their amplitude as putative Ca²⁺ plateau potentials. Furthermore, both optogenetic activation and inhibition of Chrna2 α -expressing OLM interneurons altered place cell representations at locations on the linear track where optogenetic stimulation was applied.

Taken together, our findings support the model that OLM interneurons constitute the feedback inhibitory element regulating BTSP and highlight dendrite-targeting OLM interneurons as a central signal in shaping CA1 representations during learning.

Disclosures: E.P. Campbell: None. L. Martin: None. J.C. Magee: None. C. Grienberger: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.12/JJ14

Topic: I.08. Learning and Memory

Support: NIH Grant R35NS132342
NIH Grant R01MH121372
NIH Grant R01NS104917

Title: Generative emergence of non-local representations in the hippocampus

Authors: *Y. ZHOU¹, J. SIBILLE², G. DRAGOI³;

¹Dept. of psychiatry, Yale university, New Haven, CT; ²Neurosci., AG Kremkow, Berlin, Germany; ³Psychiatry, Yale Univ., New Haven, CT

Abstract: The hippocampus is hypothesized to form a cognitive map, manifested as an internal representation of the external world. While classic place cells exhibit selective activity for specific locations within the current context, a cognitive map should also support non-local representations, which are essential for flexible navigation and planning. Non-local coding in the hippocampus is evident in theta sequences spanning from past to future locations in compressed theta cycles, experience-driven representational drift, and flickering representations between alternative future paths. However, the role of internally generated network dynamics in rapid temporal sequence coding, representational updating, and parallel recall of alternate spatial and mental navigation remains unclear. Here, we reveal rapid emergence of temporally-compressed hippocampal theta sequences in adult male rats within 1-2 laps of a novel detour via re-purposing of pre-existing correlated neuronal sequence motifs expressed during pre-detour sleep. Detour experience-induced neuronal remapping and plasticity were consolidated and reconfigured hippocampal network during post-detour sleep, which predicted future representational drift during following post-detour reversal-track runs. Pre-detour or reversal-track representations flickered with detour representation across distinct phases of theta oscillation, revealing segregation of non-local internally-generated/recalled and local experience-related hippocampal representations by theta phase. These findings demonstrate that internal generative network dynamics across brain states support rapid theta-scale sequential coding, within-day representational updating, and flickering parallel representations — collectively envisioned as forms of non-local representations — during navigation.

Disclosures: Y. Zhou: None. J. Sibille: None. G. Dragoi: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.13/JJ15

Topic: I.08. Learning and Memory

Title: The Emergence of An Abstract Cognitive Map of Reward Sequence in the Hippocampus through Learning

Authors: *Y. JIANG, X. ZHAO;
Tsinghua Univ., Beijing, China

Abstract: Generalization is a fundamental cognitive function that facilitates animals to rapidly adapt to dynamic environments. In order to do so, it requires the brain to represent abstract structures of the environment and task contingency that are invariant to specific sensory details. However, it remains poorly understood about how such abstract representation emerges during learning. To address this question, we conducted chronic two-photon calcium imaging of hippocampal CA1 pyramidal neurons in head-fixed mice performing a cue-guided structured foraging task in virtual reality. Two distinct visual cues, one associated with reward, were randomly placed at three locations on a linear track, varying on a trial-by-trial basis. We found that CA1 neuron population forms disentangled representations of cue identity and spatial location in two nearly orthogonal dimensions. Next, we introduced a novel rewarded cue into the virtual track, occupying the previously empty slot. Mice rapidly learned to perform the modified task within a few trials. Strikingly, the hippocampal representation continued to evolve in subsequent sessions, eventually forming an abstract representation of the reward sequence. This representation was preserved when the last cue was hidden or the two rewarded cues were altered, suggesting that the abstract representation may support inference and generalization. Overall, our study reveals that abstract representation of task structures evolves in the hippocampus through learning and potentially facilitates flexible transfer of learned behaviors in tasks with dynamic sensory cues.

Disclosures: Y. Jiang: None. X. Zhao: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.14/Web Only

Topic: I.08. Learning and Memory

Support: Bial Foundation Grant Programme 2022/23 A-38431

Title: Hippocampal reorganization reflects social graphs formed through passive narrative exposure

Authors: *F. SANTACROCE¹, G. COMMITTERI¹, M. TULLO², R. DI MATTEO¹, D. DI CENSO², C. SESTIERI², A. TOSONI¹;

¹Dept. of Psychology, G. d'Annunzio Univ. of Chieti-Pescara, Chieti, Italy; ²Dept. of Neuroscience, Imaging and Clin. Science, G. d'Annunzio Univ. of Chieti-Pescara, Chieti, Italy

Abstract: The hippocampus is classically known for supporting spatial navigation and episodic memory, but growing evidence suggests that it also encodes and organizes abstract experiences in structured, map-like formats. Recent works have shown that the hippocampal-entorhinal system can construct abstract knowledge via spatial codes represented in predefined low-

dimensional maps (Bellmund et. al., 2018; Park et.al., 2020) and/or cognitive transition graphs (i.e. temporal sequences) implicitly acquired (Garvert et al., 2017; Peer et. al., 2021). However, it remains unclear whether such non-spatial, abstract representations can emerge spontaneously from multidimensional, narrative experience and reflect meaningful, individualized knowledge. Here, we asked whether the hippocampus encodes participant-specific social structures learned implicitly through passive narrative exposure. Twenty-two adults first underwent a baseline fMRI session in which they viewed static pictures of unfamiliar characters extracted from two television series, while performing an orthogonal target-detection task. Over the following five days, participants watched one of the two series, passively acquiring knowledge about the characters' social relationships. They then completed a second, identical fMRI session - now after prior exposure to characters from one of the two series - and no explicit memory task. After scanning, participants rated the perceived social closeness between all character pairs. Multivoxel activation pattern for each character was modeled across both sessions, and a delta similarity matrix reflecting representational change was computed. The representational similarity analysis revealed that the reorganization of BOLD activity in the left hippocampus significantly reflected each participant's behavioral social graph ($Z = 0.90$, $pFDR = 0.004$). Additionally, univariate contrasts showed that pre-learning film differences elicited occipital responses, while post-learning activity shifted toward the precuneus, suggesting higher-order narrative integration. These findings demonstrate that the hippocampus encodes rich, conceptual social structures implicitly acquired through a naturalistic exposure to a complex narrative. This extends cognitive map theory by showing that graph-like representations in the hippocampus are not limited to abstract transitions or spatial layouts but can capture personally constructed social knowledge, supporting a flexible, domain-general relational mapping function.

Disclosures: F. Santacroce: None. G. Committeri: None. M. Tullo: None. R. Di Matteo: None. D. Di Censo: None. C. Sestieri: None. A. Tosoni: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.15/JJ16

Topic: I.08. Learning and Memory

Support: IBS-R001-D3
NRF-2012R1A3A1050385

Title: Astrocyte contacts with memory-encoding neurons change depending on memory state

Authors: *H. PARK¹, J. KIM¹, J.-I. KIM², Y. SUNG¹, H. LEE¹, B.-K. KAANG¹;

¹Inst. for basic science, Deajeon, Korea, Republic of; ²Dept. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: While engram cells have been widely studied as the cellular substrates of memory storage, emerging evidence suggests that astrocytes also contribute to synaptic plasticity and memory processing. However, the structural association between astrocytes and memory-encoding engram cells remains elusive. To address this, we developed astrocyte-enhanced green fluorescent protein reconstitution across synaptic partners (astrocyte-eGRASP) to visualize astrocyte-neuron contact and validated this tool under both in vitro and in vivo conditions. Using astrocyte-eGRASP, we observed an engram-specific increase in astrocyte-neuron contacts following memory formation, which was not observed after extinction. These findings demonstrate that astrocyte-engram cell interactions vary with memory state and suggest a structural basis for the involvement of astrocytes in dynamic memory process.

Disclosures: H. Park: None. J. Kim: None. J. Kim: None. Y. Sung: None. H. Lee: None. B. Kaang: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.16/JJ17

Topic: I.08. Learning and Memory

Title: Retroactive Brain Activity Balances Memory and Forgetting

Authors: *L. AN, H. WANG;
Physiol., Michigan State Univ., East Lansing, MI

Abstract: Forgetting is a fundamental component of memory formation, actively shaping memory traces and contributing to their eventual decay. Despite its recognized importance, the neurobiological and cellular mechanisms underlying forgetting remain poorly understood. In this study, we investigated how retroactive neuronal activity within a specific brain region orchestrates activity-dependent forgetting. We found that novelty exploration (NE) *after*, but not *before* learning induces active forgetting and impairs object location memory (OLM). Post-learning activation of NE-associated neurons in the dorsal hippocampus (dHip) similarly disrupted OLM, whereas suppressing dHip activity during post-learning NE preserved memory. Notably, direct inhibition of basal dHip activity following learning enhanced OLM performance. *In vivo* single-cell calcium imaging revealed that dHip neurons activated during object location learning are reactivated during memory recall. However, in mice exposed to post-learning NE, NE-activated neurons co-fired with learning-activated neurons, contaminating the original engram and impairing recall. Together, these findings identify cellular substrates of active forgetting and underscore the critical, time-sensitive role of region-specific retroactive brain activity in mediating the balance between memory preservation and decay.

Disclosures: L. An: None. H. Wang: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.17/JJ18

Topic: I.08. Learning and Memory

Support: DFG 509099330
DFG 514483642

Title: Ageing shifts the composition of the hippocampal inhibitory engram

Authors: W. FERNANDES PAES DE BARROS¹, S. SWER¹, C. ELGUETA², C. B. DEAN³, S. VIANA DA SILVA³, ***M. HABERL**⁴;

¹Charité Universitätsmedizin, Berlin, Germany; ²Freiburg Univ., Freiburg Im Breisgau, Germany; ³DZNE, Berlin, Germany; ⁴Charite Universitätsmedizin Berlin, Berlin, Germany

Abstract: Inhibitory interneurons have fundamental roles in shaping neural circuits and synaptic plasticity within the hippocampus, a brain region critical for memory encoding and consolidation. However, the participation of hippocampal interneurons in the spatial engram has received few attention thus far. We use the immediate early gene FOS as a marker of engram cells and characterize the effect of ageing on the hippocampal engram in CA1, CA3, and DG of the hippocampus, following exposure to environmental enrichment in comparison to standard housing conditions. To identify interneuron subtypes we used markers for specific interneuron subpopulations (SOM, PV, VIP, CCK) to assess their participation in engram formation. We identify a critical shift in the I/E ratio of the engram composition throughout increasing age. Our findings have significant implications for understanding the physiology of memory in the ageing brain.

Disclosures: W. Fernandes Paes de Barros: None. S. Swer: None. C. Elgueta: None. C.B. Dean: None. S. Viana Da Silva: None. M. Haberl: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.18/JJ19

Topic: I.08. Learning and Memory

Support: Italian National Recovery and Resilience Plan (NRRP), M4C2, funded by the European Union – NextGenerationEU (Project IR0000011, CUP B51E22000150006, “EBRAINS-Italy”) EU Horizon Europe Program under the specific Grant Agreement

101147319, EBRAINS 2.0 project.

PRIN 2022ZY5RXB CUP E53D2301172 Data driven implementation of a computational model for the human hippocampus - HIPPOCOMP

Title: Exploring Mouse Hippocampal CA1 network behavior through large-scale simulations

Authors: *E. GIACALONE^{1,3}, E. SPERA^{2,4}, D. GANDOLFI⁵, C. LUPASCU⁷, J. MAPELLI⁶, G. BOIANI⁸, S. GIBERTI⁹, S. M. SOLINAS¹⁰, L. BOLOGNA¹¹, A. MARASCO¹², M. MIGLIORE¹³;

²Inst. of Biophysics, ¹Natl. Res. Council, CNR, Palermo, Italy; ³Mathematics and Computat. Sci., Univ. of Palermo, Palermo, Italy; ⁴Natl. Res. Council, Palermo, Italy, Palermo, Italy; ⁵Dept. of Brain and behavioral sciences, Univ. di Pavia, Pavia, Italy; ⁶Univ. di Pavia, PAVIA, Italy; ⁷Natl. Res. Council, Inst. of Biophysics, Palermo, Italy; ⁸Dept. of Biomedical, Metabolic and Neural Sci., ⁹Univ. of Modena and Reggio Emilia, Modena, Italy; ¹⁰Dept. Of Biomed. Sci., Univ. of Sassari, Sassari, Italy; ¹¹CNR, Palermo, ; ¹²Mathematics and Applications, Univ. of Naples Federico II, Napoli, Italy; ¹³Inst. of Biophysics, Natl. Res. Council, Palermo, Italy

Abstract: Building biologically realistic models of brain circuits is a central challenge in computational neuroscience. Accurate representations of specific regions, such as the hippocampus, are essential to investigate both physiological functions and pathological mechanisms. However, achieving biologically detailed large-scale simulations while maintaining computational efficiency remains a major challenge. We present a biologically plausible full-scale model of the mouse hippocampal CA1 region, implemented in the NEST simulator. The network includes A-GLIF models for pyramidal neurons and interneurons, using a custom cloning procedure to reproduce the experimentally observed heterogeneity of intrinsic properties [Marasco et al. 2023, Marasco et al. 2024]. Connectivity is established via a geometric probability-based method, enabling the construction of a network with plausible connectivity patterns in good agreement with experimental findings [Gandolfi et al. 2022]. The synaptic model's parameters were tuned according to experimental data to ensure realistic synaptic transmission dynamics [Ecker et al. 2020]. In this poster, we show how the model was used to perform simulations under various physiological and perturbed conditions. The results highlight the emergence of distinct network characteristic frequencies as a function of connectivity weights and external stimulation, and demonstrate how cellular and synaptic variability critically influences network behavior. Moreover, the model is capable of reproducing the physiological behavior of the CA1 network in terms of mean firing rates as well as the characteristic frequencies that define network activity. Through analysis of firing variations, the model opens the way to a more detailed investigation of the underlying mechanisms driving changes in neuronal firing. Furthermore, the simulations explored how variations in network heterogeneity modulate the activity of the CA1 circuit, highlighting the critical role of biological diversity in shaping network behavior. Overall, the model provides a robust and reproducible platform for investigating both normal function and dysfunction of the hippocampal CA1 region.

Disclosures: E. Giacalone: None. E. Spera: None. D. Gandolfi: None. C. Lupascu: None. J. Mapelli: None. G. Boiani: None. S. Giberti: None. S.M. Solinas: None. L. Bologna: None. A. Marasco: None. M. Migliore: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.19/JJ20

Topic: I.08. Learning and Memory

Support: European Union's Horizon Europe research and innovation programme under grant agreement No 101147319 (EBRAINS 2.0). Italian National Recovery and Resilience Plan (NRRP), M4C2, funded by the European Union - NextGenerationEU (Project IR0000011, CUP B51E22000150006, "EBRAINS-Italy") PRIN 2022ZY5RXB CUP E53D2301172 Data driven implementation of a computational model for the human hippocampus - HIPPOCOMP

Title: From Silent Synapses to Loud Rhythms: Simulating the Circuit Impact of AETA Deficiency

Authors: *A. CORREA LUCES^{1,2}, A. P. PONZI³, H. MARIE⁴, M. MIGLIORE⁵;
¹IBF - CNR, Palermo, Italy; ²Natl. Res. Council, CNR, Palermo, Italy; ³Ctr. for Human Nature, Artificial Intelligence, and Neurosci. (CHAIN), Hokkaido Univ., Hokkaido, Japan; ⁴Inst. de Pharmacologie Moléculaire et Cellulaire (IPMC), Valbonne, France; ⁵Inst. of Biophysics, Natl. Res. Council, Palermo, Italy

Abstract: Alterations in phase-amplitude coupling (PAC) have also been observed in APP^{ΔE299} mice, a model lacking the AETA peptide, particularly during REM sleep when hippocampal theta rhythms are prominent. AETA is a newly identified peptide produced through APP cleavage, specifically active at synapses containing NMDA receptors (NMDARs), a class of glutamate-gated ion channels essential for regulating synaptic strength. It uniquely inhibits NMDAR ionotropic activity while promoting ion-flux-independent synapse weakening (Dunot et al, "APP fragment controls both ionotropic and non-ionotropic signaling of NMDA receptors" 2024). AETA is also essential for proper NMDAR signaling, which is important for long-term depression and memory processing. Ex vivo studies in a knock-out mouse model of AETA revealed increased NMDAR signaling and a rise in NMDAR-only (silent) synapses within CA1 pyramidal neurons. To investigate how this can alter network dynamics, we used a computational model of hippocampal microcircuits based on the framework described in "Theta-gamma phase amplitude coupling in a hippocampal CA1 microcircuit. PLOS Computational Biology" Ponzi et al.(2023), incorporating biologically grounded neuron and synapse types. We implemented parameter changes derived from the experimental findings, including enhanced NMDAR signaling and reduced AMPAR/NMDAR ratios, and systematically explored their impact on emergent network activity. We analyzed phase amplitude coupling (PAC), power spectra, and band-specific power (theta, gamma) across model conditions. Our results show that synaptic changes driven by AETA loss are sufficient to modulate PAC and shift the spectral profile of network activity. These findings support a causal role for NMDAR-mediated synaptic remodeling in shaping large-scale oscillatory signatures. Given the link between APP processing

and Alzheimer's disease (AD), our study may help clarify how NMDA dysfunction contributes to hippocampal oscillations in AD.

Disclosures: A. Correa Lucas: None. A.P. Ponzi: None. H. Marie: None. M. Migliore: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.20/JJ21

Topic: I.08. Learning and Memory

Support: Brain Canada - Azrieli Foundation
Canada Foundation for Innovation - JELF - 44845

Title: Hippocampal interneuron dysfunction in sensory encoding and working memory in a mouse model of schizophrenia

Authors: *M. GERLAI^{1,2}, J. DUDA¹, T. LIU¹, J. TAXIDIS²;

¹Physiol., Univ. of Toronto, Toronto, ON, Canada; ²Neurosci. and Mental Hlth., The Hosp. For Sick Children, Toronto, ON, Canada

Abstract: Schizophrenia (SZ) is characterized by working memory (WM) deficits, believed to be underpinned by aberrant hippocampal (HPC) inhibitory signaling. Dysfunctional parvalbumin (PV) and somatostatin (SST) interneuron dynamics have been reported in the Df(16)A+/- (Df16A) mouse model, a model of the human 22q11.2 chromosomal deletion, a strong predictor of SZ. However, physiological deficits of these fast-spiking inhibitory microcircuits are poorly understood in-vivo, and in relation to non-spatial WM paradigms. Therefore, during an olfactory WM task, we performed in-vivo voltage imaging on double transgenic PV-Cre and SST-Cre Df16A mice. We recorded spike and subthreshold activity of PV and SST interneurons in the dorsal CA1 at a high temporal resolution (500 frames/sec) with a large field of view. By recording longitudinally across days, learning-dependent deficits in inhibitory signaling may be revealed. Our ongoing analyses compare PV and SST spiking and subthreshold dynamics compared to littermate controls. Notably, aberrant interneuron synchronous activity and sub-second subthreshold dynamics at odor onset in Df16A mice may disrupt stimulus-specific activation of CA1 pyramidal neurons. Noisy stimulus encoding may ultimately result in observed WM deficits. These experiments will reveal how interneuron dysfunction leads to disruption of WM processes in SZ, with implications for HPC inhibitory circuits as future therapeutic targets.

Disclosures: M. Gerlai: None. J. Duda: None. T. Liu: None. J. Taxidis: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.21/JJ22

Topic: I.08. Learning and Memory

Support: Brain Canada - Azrieli Foundation
Canada Foundation for Innovation - JELF - 44845

Title: Behavioral time-scale synaptic plasticity leads to odour memory representation in CA1.

Authors: *J. DUDA^{1,2}, A. I. RAMSARAN², T. LIU^{1,2}, M. GERLAI^{1,2}, J. TAXIDIS^{2,1};
¹The Univ. of Toronto, Toronto, ON, Canada; ²Neurosci. and Mental Hlth., The Hosp. for Sick Children, Toronto, ON, Canada

Abstract: The brain forms memories by building connections between neurons whose firing encodes related concepts. For example, mental maps needed for navigation can be formed of cells representing specific locations. Recently, it was found that hippocampal neurons which underwent a depolarization event called a “plateau potential” could rapidly tune their firing to specific locations. This phenomenon, titled behavioral time scale synaptic plasticity (BTSP), may thus act as a mechanism for the hippocampus to rapidly form spatial memories. However, it remains unclear if BTSP can tune neurons to sensory cues or abstract concepts to build representations of non-spatial experiences (remembering a grocery list for example). To investigate this, we first performed 2-photon calcium imaging of pyramidal neurons in the CA1 hippocampal subregion of CamK2a-Cre transgenic mice during an odour discrimination task where mice are trained to recognize certain odours as rewarded. We present neurons which underwent a plateau potential and subsequently showed firing patterns specific to odour presentation. We then performed 1-photon voltage imaging of pyramidal cells in these mice, during the same task, which uniquely allowed us to describe the subthreshold properties of plateau potentials and to analyze the dynamics of neurons before they showed tuned firing. Finally, to further confirm that BTSP was leading to the formation of odour cells, we performed simultaneous calcium imaging and holographic optogenetic stimulation of single cells, in order to produce artificial “plateau potentials” by driving strong depolarizations. This was done while mice performed the odour discrimination task in an attempt to drive the formation of odour tuned cells, analogous to how place cells have been artificially formed in previous experiments. Our results demonstrate that BTSP can tune cells to non-spatial stimuli which could then be integrated into larger networks representing relationships between odours and rewards. This suggests that BTSP is not limited to forming spatial maps but instead is a leading candidate for the mechanism behind the rapid neural plasticity needed to form a hippocampal representation of episodic experiences as they happen.

Disclosures: J. Duda: None. A.I. Ramsaran: None. T. Liu: None. M. Gerlai: None. J. Taxidis: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.22/KK1

Topic: I.08. Learning and Memory

Support: NSERC RGPIN-2024-05568
Canada Foundation for Innovation - JELF - 44845

Title: Vip interneuronal dynamics in memory-encoding hippocampal spiking sequences

Authors: *T. K. LIU^{1,2}, J. TAXIDIS²;

¹Dept. of Physiol., Univ. of Toronto, Toronto, ON, Canada; ²Neurosciences and Mental Hlth. Program, The Hosp. For Sick Children, Toronto, ON, Canada

Abstract: Episodic memory relies on the spiking sequences of pyramidal neurons in the hippocampus to encode spatiotemporal contexts. Such sequences are tightly regulated by inhibitory GABAergic interneurons, including parvalbumin (PV), somatostatin (SST) and vasoactive intestinal polypeptide (VIP) expressing cells. PV/SST cells provide direct somatic and dendritic inhibition on pyramidal cells respectively, while VIP cells inhibit PV/SST cells, thus ‘disinhibiting’ pyramidal neurons. This integrated network ensures precise spiking sequences and maintains the excitation/inhibition (E/I) balance, critical for memory encoding and temporal organization. Although PV/SST-mediated inhibition has been extensively explored, VIP-mediated disinhibition remains poorly understood, especially within the hippocampal CA1 area. Here we investigated how VIP-mediated disinhibition contributes to the memory encoding in hippocampal CA1, using *in vivo* voltage imaging with genetically encoded voltage indicators (GEVIs). To characterize VIP dynamics during diverse sensory inputs and locomotion outside memory activation, we first described VIP activity in CA1 of untrained VIP-Cre mice during head-fixed treadmill running and randomized delivery of olfactory cues, auditory cues and water rewards. We then described VIP membrane potentials during an odor-cued working memory task. We have previously shown increased PV/SST activation during odor cues, preceded by a sharp hyperpolarization at cue onset, with both features regulating pyramidal spiking sequences (Taxidis et al., 2020; 2023). Hence, we focused on VIP dynamics at cue delivery and particularly at cue onset, to elucidate temporal relationships between VIP activity and memory-encoding pyramidal sequences. Our findings shed light on the role of VIP-mediated disinhibition in shaping pyramidal spiking sequences and provide insights into inhibitory circuits during hippocampal memory encoding.

Disclosures: T.K. Liu: None. J. Taxidis: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.23/KK2

Topic: I.08. Learning and Memory

Support: SickKids Restrcomp
CanNRT Platform

Title: Statistical learning in the mouse hippocampus

Authors: *A. I. RAMSARAN¹, S. A. JOSSELYN², P. W. FRANKLAND³, J. TAXIDIS⁴;
²Neurosci. & Mental Hlth., ³PGCRL - NMH 5th floor, ⁴Neurosciences and Mental Hlth., ¹The Hosp. For Sick Children, Toronto, ON, Canada

Abstract: Neuronal activity in the mammalian hippocampus is essential for encoding episodic memories, i.e., memories for experienced events and their spatiotemporal contexts. In addition to supporting this highly-specific form of memory, neuroimaging and behavioral studies conducted with human participants demonstrate a role for the hippocampus in statistical learning, or the extraction of regularities across experiences. Importantly, these studies suggest that statistical learning within the hippocampus can occur rapidly and incidentally (i.e., without explicit reinforcement). While the mechanisms supporting episodic memory in the hippocampus have been explored extensively, how the hippocampus learns statistical regularities from stimuli remains poorly understood. Here, we examined statistical learning in the hippocampus of Thy1-GCaMP6f transgenic mice using two-photon imaging. Inspired by tasks used to assess statistical learning in the human hippocampus, we exposed mice to structured or unstructured sequences of odor stimuli while recording calcium activity from CA1 neurons across days. We describe longitudinal changes in CA1 odor representations in mice that experienced structured odor sequences, consistent with latent statistical learning within the hippocampus. Such representations may enable memory-guided prediction or associative inference supported by the hippocampus.

Disclosures: A.I. Ramsaran: None. S.A. Josselyn: None. P.W. Frankland: None. J. Taxidis: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.24/KK3

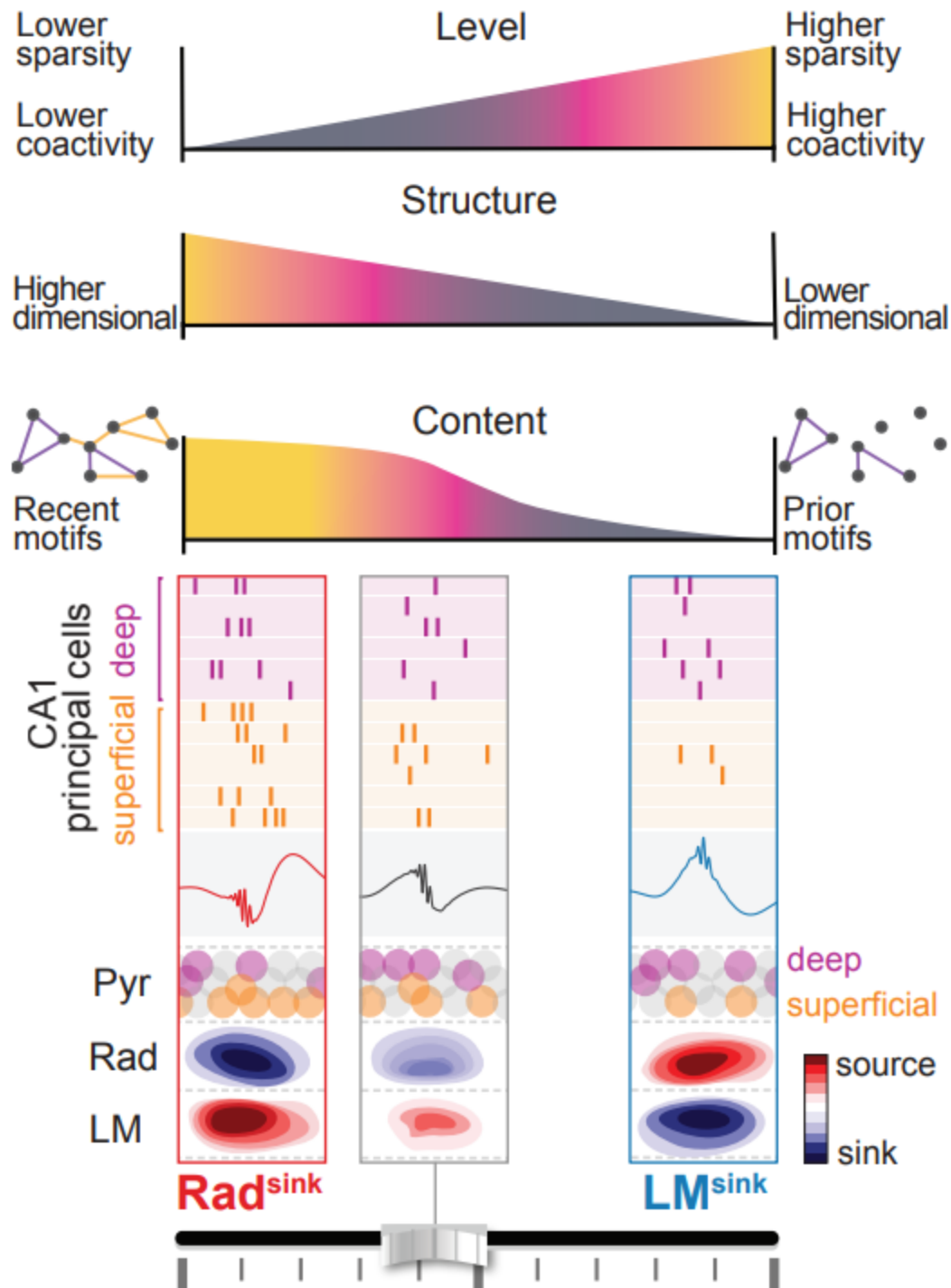
Topic: I.08. Learning and Memory

Support: Medical Research Council (MRC) UK studentship (MC_ST_BNDU_2019) to M.C.
Medical Research Council (MRC) UK Transition to post-doc (MR/W006731/1) to M.C.
Medical Research Council (MRC) UK (Programmes MC_UU_12024/3, MC_UU_00003/4, and MR/W004860/1 to D.D.)

Title: Hippocampal Ripple Diversity organises Neuronal Reactivation Dynamics in the Offline Brain

Authors: *M. CASTELLI, V. LOPES DOS SANTOS, G. GAVA, D. DUPRET;
Nuffield Dept. of Clin. Neurosciences, MRC Brain Network Dynamics Unit at the Univ. of Oxford, Oxford, United Kingdom

Abstract: Hippocampal ripples are highly synchronized neuronal population patterns reactivating past waking experiences in the offline brain. Whether the level, structure, and content of ripple-nested activity are consistent across consecutive events or are tuned in each event remains unclear. By profiling individual ripples using laminar currents in the mouse hippocampus during sleep/rest, we identified Radsink and LMsink ripples featuring current sinks in stratum radiatum versus stratum lacunosum-moleculare, respectively. These two ripple profiles recruit neurons differently. Radsink ripples integrate recent motifs of waking coactivity, combining superficial and deep CA1 principal cells into denser, higher-dimensional patterns that undergo hour-long stable reactivation. In contrast, LMsink ripples contain core motifs of prior coactivity, engaging deep cells into sparser, lower-dimensional patterns that undergo a reactivation drift, gradually updating their pre-structured content for recent wakefulness. We propose that ripple-by-ripple diversity instantiates parallel reactivation channels for stable integration of recent wakefulness and flexible updating of prior internal representations.



Disclosures: M. Castelli: None. V. Lopes Dos Santos: None. G. Gava: None. D. Dupret: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.25/KK4

Topic: I.08. Learning and Memory

Support: BB/S007741/1
BB/N002547/1
MC_UU_00003/4

Title: Characterising the hippocampal network coactivity dynamics across different mnemonic processes

Authors: *G. GAVA¹, D. DUPRET²;

¹Univ. of Oxford, Oxford, United Kingdom; ²MRC BNDU, Univ. of Oxford, Oxford, United Kingdom

Abstract: The hippocampus is a critical region involved in memory formation and related processes, believed to support them through the precise temporal coordination of its neuronal population. In previous work, we revealed how such hippocampal network dynamics can be captured by its coactivity topology. In this study, we leverage this framework together with dynamical systems and topology tools to investigate how the network operational regime changes in response to different mnemonic processes, such as encoding and retrieval. We employ an ephys dataset composed of CA1 neurons from hippocampal CA1 recorded in mice exploring familiar and novel environments (Fig 1a). The rodent hippocampal network is well known to display different oscillatory activity patterns believed to support distinct memory processes: awake periods are characterised by prominent theta oscillations and have been related to memory encoding, while sleeping is characterised by slow wave oscillations interrupted by brain-wide sharp-wave-ripple events (SWRs), associated to the consolidation of memories (Fig 1b). I propose to characterise the operational regime of these two neural states by capturing the coactivity during theta-bouts or SWRs (Fig 1c). Preliminary results suggest that the distribution of coactivity relations in the network gets narrower during the exploration of novel environments, together with a decrease in sparsity and an increase in dimensionality of the neuronal activity (Fig 1d-f). These suggest that the coactivity topology of the network becomes more akin to a random network, possibly a more malleable state ready for the encoding of new information. These could be hallmarks of a more subcritical, noisy operational regime. By capturing the network coactivity during SWRs, I aim to characterise the operational regime of the system across sleep, possibly relating it to its homeostatic function.

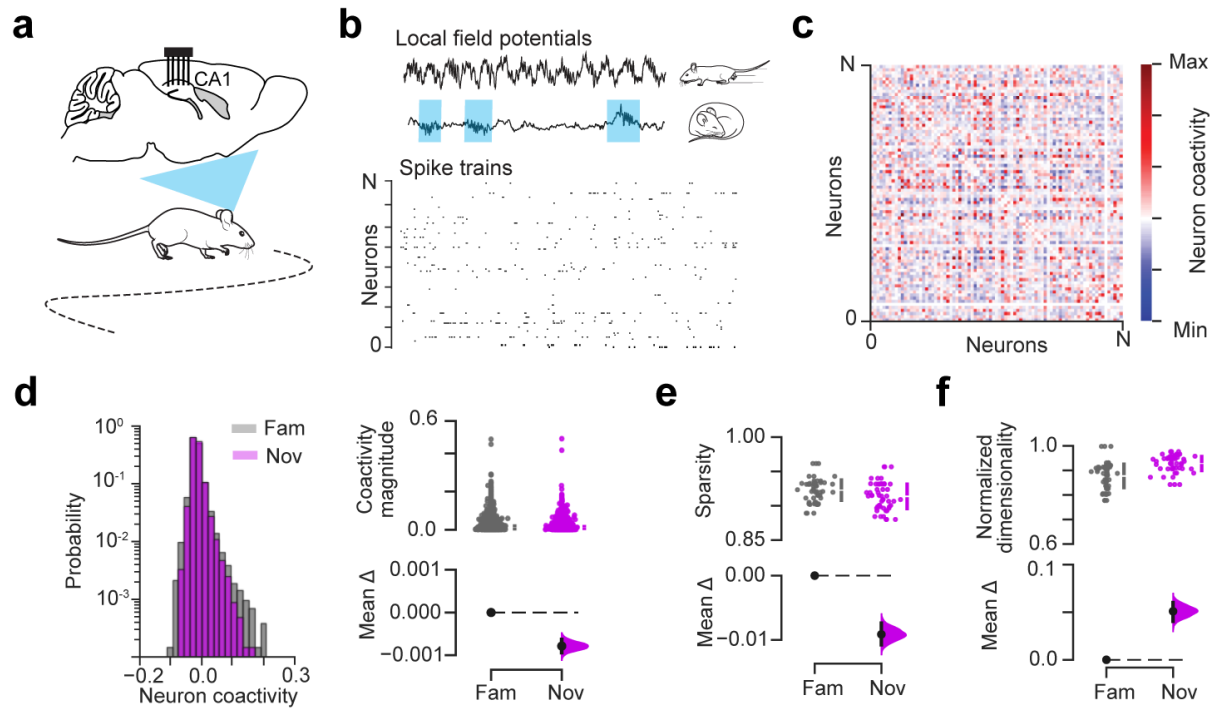


Figure 1: Coactivity framework for the analysis of hippocampal electrophysiological data.

Disclosures: G. Gava: None. D. Dupret: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.26/KK5

Topic: I.08. Learning and Memory

Support: NIH MH120406

Title: Dynamic co-recruitment of rhythmic activity in the hilus and granule cell layer of the dentate gyrus during learning and recall

Authors: *A. K. LEISCHING¹, K. YU², Y. WANG³, N. GAO⁴, L. M. RANGEL¹;
¹Cognitive Sci., UCSD, La Jolla, CA; ²Stanford Univ., Stanford, CA; ³Biochem. and Mol. Biol., Johns Hopkins Univ., Baltimore, MD; ⁴Computat. Biol. and Bioinformatics, Yale Univ., New Haven, CT

Abstract: When similar experiences yield distinct outcomes, memory systems must disambiguate the overlapping contextual features of each experience to ensure that future actions are guided by the appropriate past experiences. The hippocampal dentate gyrus (DG) is thought to reduce memory interference by generating unique representations of experience, particularly

in contexts where similar spatial cues must be associated with distinct outcomes. However, little is known about how the DG's intrinsic circuitry is leveraged to support this process across learning and recall. To investigate this, we conducted *in vivo* electrophysiological recordings using laminar probes spanning the DG granule cell and hilar layers. In our study, rats (N = 3) performed a spatial reward association task with distinct learning and recall phases. Both granule cell and hilar layers were co-recruited into 20-40 Hz gamma rhythmic activity during key path selection and outcome intervals of our task. Notably, incorrect choices during recall phases were preceded by a stereotyped reduction in 20-40 Hz activity during the path selection epochs of learning phases. Our findings suggest that rhythmic coordination across granule cell and hilar layers may be essential for forming distinct spatial reward associations during learning.

Disclosures: A.K. Leisching: None. K. Yu: None. Y. Wang: None. N. Gao: None. L.M. Rangel: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.27/KK6

Topic: I.08. Learning and Memory

Support: NSF DMS-1042134
NIH MH052090
NIH MH120406

Title: The binding of spatial and sensory cue information in dentate gyrus and CA1 during associative memory processing

Authors: *C. R. HEYMAN¹, B. S. PORTER², I. S. HEIMBUCH³, L. M. RANGEL⁴;
¹Neurosci., Univ. of Utah, Salt Lake City, UT; ²Psychology, Brandeis Univ., Waltham, MA;
³Neurol., UCSF, San Francisco, CA; ⁴Cognitive Sci., UCSD, La Jolla, CA

Abstract: Associative memory requires an ability to bind different features of an experience together. In the hippocampus, a brain region important for learning and memory, this manifests at the cellular level in subregions CA3 and CA1 through activity that is selective for the co-occurrence of multiple features of experience, which is termed *conjunctive encoding*. The dentate gyrus (DG) is the first site of cortical convergence in the hippocampus, positioning it ideally to bind distinct aspects of experience in a manner that powerfully influences other hippocampal subregions. To date, little is known regarding how conjunctive representations in DG differ from those in other hippocampal subregions, which would provide insight into the unique roles of each subregion. We performed *in vivo* electrophysiological recordings (N=5 male Long-Evans rats) from the DG and CA1 subregions of the hippocampus as rats performed a context-guided odor-reward association task in which pairs of odors were rewarded depending upon the context in which they were presented. This task allowed us to determine the extent that DG (N=81) and

CA1 (N=414) cell spiking activity contained information for rat position, odor identity, and their conjunctions. We found that a substantial proportion of cells from both regions contained information in their spiking activity for rat position, odor identity, and odor-position conjunctions. However, a substantially larger proportion of CA1 cells with conjunctive encoding abilities also maintained significant information for individual positions and odor identities. Our results suggest different frameworks within DG and CA1 for binding spatial and olfactory information.

Disclosures: C.R. Heyman: None. B.S. Porter: None. I.S. Heimbuch: None. L.M. Rangel: None.

Poster

PSTR045: Intrinsic Hippocampal Circuits

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR045.28/KK7

Topic: I.08. Learning and Memory

Support: National Institutes of Health grant R01MH1105142
National Institutes of Health grant R03MH120406
National Institutes of Mental Health MH052090
National Science Foundation DMS-1042134
National Science Foundation Science of Learning Center grant SBE 0542013, Temporal Dynamics of Learning Center
Kavli Institute for Brain and Mind (LMR, PDR)

Title: The temporal order of CA1 interneuron entrainment to multiple rhythmic circuits

Authors: *I. ZANE¹, P. D. RIVIERE³, L. M. RANGEL²;

¹Cognitive Sci., UCSD, San Diego, CA; ²Cognitive Sci., UCSD, La Jolla, CA; ³Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Inhibition constitutes an essential organizing property of many biological systems. In the brain, inhibitory interneurons impose temporal constraints upon neuronal interactions at multiple, often rhythmic time scales. The extent to which interneurons play multiple, potentially evolving, roles given changing inputs or behavioral states is currently not well understood. In our work, we describe a structure to the roles that interneurons play across multiple rhythmic subcircuits in the hippocampus. We acquired in vivo electrophysiological recordings from the CA1 subregion of the hippocampus (N = 5 rats) as rats performed a context-guided odor-reward association task. We demonstrate that inhibitory interneurons cluster by the timing of their activity within rhythms, and that the timing of hippocampal CA1 interneuron spiking activity within the 4-12 Hz theta rhythm predicts the timing of their activity in 35-55 Hz low and 65-90 Hz high gamma rhythms. Co-recruitment into multiple rhythmic circuits was behaviorally dependent, as a highly structured recruitment into theta-low gamma rhythmic circuit activity

occurred selectively during odor cue sampling, and not high locomotion, epochs. Changing behavioral states and sensory inputs altered the degree of interneuron recruitment into each rhythm, but interneurons maintained consistent timing preferences within each rhythm when recruited. Our results suggests that 1) there is a temporal order to inhibitory contributions within rhythmic circuits, 2) that particular rhythmic circuit interactions are linked by shared inhibitory interneurons contributions, and 3) that interneurons do not vary the temporal order of their contributions to rhythmic circuits in the face of changing inputs or behavioral states. Instead, changing inputs or behavioral states determine whether interneurons are recruited at all into rhythmic circuit interactions, but do not change their roles if they are recruited. Taken together, our study suggests that exquisite timing in multiple rhythms is not random, but highly structured.

Disclosures: **I. Zane:** None. **P.D. Riviere:** None. **L.M. Rangel:** None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.01/KK8

Topic: I.08. Learning and Memory

Support: NIH Grant DA020041

Title: Dose-effect analysis of 6-APB ("Benzofury") on fear memory, motor behavior, and reward-seeking behaviors

Authors: ***K. WHITELOCK**¹, K. VAN ALSTYNE¹, L. CONABOY¹, J. KIM¹, S. G. ANAGNOSTARAS²;

²Psychology & Neurosciences, ¹UCSD, San Diego, CA

Abstract: 6-(2-aminopropyl)benzofuran (6-APB) is a new psychoactive substance (NPS) that is structurally similar to MDMA. There is currently very little known about the behavioral effects of 6-APB and its dose-effect relationship. As the popularity of NPS, such as 6-APB, increases due to their unscheduled status and easy availability online, it is important to understand the potential benefits and/or harms of such substances. We found that 6-APB elicits behavioral effects at very low doses (0.01 and 0.1 mg/kg) and impairs short- and long-term memory at higher doses. Furthermore, 6-APB produced apparent motor deficits, including reduced rearing, jumping, and impaired motor skill acquisition and retention on the accelerating rotarod. Finally, results from conditioned place preference suggest that 6-APB is modestly reinforcing and may produce addiction. Overall, 6-APB produced effects similar to MDMA, but with higher potency and a pronounced motor impairment, suggesting it should be further regulated.

Disclosures: **K. Whitelock:** None. **K. Van Alstyne:** None. **L. Conaboy:** None. **J. Kim:** None. **S.G. Anagnostaras:** None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.02/KK9

Topic: I.08. Learning and Memory

Support: University funding

Title: The effects of hydroxycitric acid on weight, memory, and adiposity in rats

Authors: *H. M. MURPHY¹, C. H. WIDEMAN²;

²Biol., ¹John Carroll Univ. Interdisciplinary Neurosci. Concentration, University Heights, OH

Abstract: Over the years, obesity has presented itself as a growing threat to many Americans. Issues of obesity in the United States have been around since the early 1950s, but recently has become an escalating and problematic public health concern. Many obese Americans have turned to dietary supplements in hopes of improving their health and body image. There are numerous dietary supplements on the market but, unlike drugs, dietary supplements are not as strictly regulated by the FDA. In *Garcinia cambogia* supplement, the major chemical identified is hydroxycitric acid (HCA) which has been implicated in reducing obesity, influencing memory, and decreasing adiposity. Research utilizing HCA has provided mixed results regarding these variables. In the present study, rats were utilized to examine metabolic and memory effects of the supplement and it was hypothesized that the administration of *Garcinia cambogia* would produce a decrease in gain of body weight and adiposity and that memory would be enhanced. Twelve male Long Evans rats (6 control animals, 6 experimental animals) were studied. A 12/12-hour light/ dark cycle was employed. Following a 7-day habituation period, all animals were provided with a condensed milk “treat” in the first 15 minutes of the dark cycle. During a 25-day experimental period, experimental rats were administered a 500 mg/kg body weight dose of *Garcinia cambogia* in the condensed milk and control rats were given a placebo in the condensed milk during the dark period. The Morris water maze (MWM) was utilized for testing learning and memory on days 8 through 32 of the experimental period. The MWM test consisted of two trials. In trial 1 (sample trial), the rat learned the new location of the platform by trial and error and in trial 2 (test trial), a matching trial to trial 1, a calculation of savings in recall was measured. Adiposity was examined on a scale of 1-3 following sacrifice of the animals. Hypotheses concerning body weight, memory, and adiposity were not supported in this study. In similar research, contradictory results have been observed regarding the effectiveness of the supplement. While some studies suggest potential benefits for weight management, others do not and cite evidence for induction of hepatotoxicity by the supplement. Some research indicates that the supplement can potentially affect memory while other evidence suggests the supplement might interfere with brain chemistry. Unfortunately, there is no true regulation to stop companies from selling ineffective supplements even though manufacturers are responsible for making sure that the products do not pose a risk to the consumer and that claims are not misleading.

Disclosures: H.M. Murphy: None. C.H. Wideman: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.03/KK10

Topic: I.08. Learning and Memory

Title: Neuroprotective effects of isoflavone-enriched mung bean leaf extract in a scopolamine-induced memory impairment mouse model

Authors: Y. LEE¹, M. C. ANG², *S. KANG¹;

¹Gyeongsang Natl. Univ., Jinju, Korea, Republic of; ²Basic Vet. Sci., Univ. of the Philippines Los Banos, Los Banos, Philippines

Abstract: Mung bean (*Vigna radiata*) leaves, particularly those enriched in isoflavones via metabolite farming, have emerged as promising natural sources of neuroprotective agents. This study investigated the memory-enhancing effects of isoflavone-rich mung bean leaf (I-MBL) extract on scopolamine-induced memory impairment in mice, focusing on its cholinergic modulation and antioxidant properties. I-MBL was prepared from mung bean plants treated with ethylene using a metabolite farming method, which significantly increased levels of isoflavones such as 2-hydroxydiazine and diazine, as confirmed by high-performance liquid chromatography. Male mice received oral I-MBL (10 or 30 mg/kg) for five consecutive days, followed by intraperitoneal administration of scopolamine to induce cognitive deficits. Cognitive performance was evaluated using the novel object recognition and passive avoidance tests. Biochemical analyses of brain tissue included quantification of acetylcholine (ACh) levels and acetylcholinesterase (AChE) activity. The antioxidant and anti-inflammatory capacities of I-MBL were assessed through 2,2-diphenyl-1-picryl-hydrazyl-hydrate radical scavenging and nitric oxide inhibition assays. I-MBL administration significantly ameliorated scopolamine-induced learning and memory impairments during the acquisition and retention phases. Furthermore, I-MBL treatment normalized hippocampal ACh levels and suppressed AChE activity altered by scopolamine. Notably, I-MBL exhibited strong antioxidant and anti-inflammatory activities *in vitro*. Collectively, these findings suggest that I-MBL exerts neuroprotective effects by modulating the cholinergic system and reducing oxidative stress, supporting its potential as a natural cognitive enhancer for memory-related disorders.

Disclosures: Y. Lee: None. M.C. Ang: None. S. Kang: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.04/KK11

Topic: I.08. Learning and Memory

Title: Neuropharmacological Exploration- Novel chalcone based small molecules ameliorate STZ induced memory dysfunction in mice for Cognitive Enhancement

Authors: *M. SINGH;
Chitkara University, Punjab, Rajpura, India

Abstract: Background: One of the leading causes of dementia is Alzheimer's disease, which initiated via plethora of biochemical alterations in brain of which Cholinergic, oxidative stress, and advance glycation end products (AGEs) have been identified as key mediators. Thus, the development of drugs targeting these pathways may help in managing AD. **Method:** Novel aminoalkylchalcone based molecules were designed and synthesized using aldol condensation method. *In silico* predication analysis was taken to determine the interactions of synthesized drugs with acetylcholinesterase. Memory enhancing effects were determined *in-vivo* for most potent molecule against Streptozotocin induced memory deficit in mice. Possible mechanisms were studied by determining various brain biochemical parameters. **Result:** Novel aminoalkylchalcones were synthesized and showed strong interactions with crucial amino acids of target protein. Additionally, syntheses molecules showed strong AChE, DPPH and AGEs inhibitory activity determined *in vitro*. Furthermore, these novel compounds reversed STZ induced cognitive deficit (Morris water maze test) as well as oxidative stress, cholinergic hyperactivation and AGEs formation. **Conclusion:** Aminoalkylchalcones had potential to improve the cognitive functions via improving cholinergic transmission and reducing oxidative stress and AGEs. Thus, these potential molecules could be taken for further studies including toxicity evaluation to develop them as anti-Alzheimer's disease drugs.

Disclosures: M. Singh: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.05/KK12

Topic: I.08. Learning and Memory

Support: Indian Council of Medical Research (ICMR), 5/4/5-11/Diab./20-NCD-III)

Title: Pharmacological modulation of SIRT3 ameliorates the type 2 diabetes associated cognitive impairment by upregulating hippocampal neurogenesis through Wnt 3a/ β -catenin pathway

Authors: *D. S. PADHY¹, S. BANERJEE²;

¹Pharmacol. and Toxicology, NIPER Kolkata, Kolkata, India; ²Pharmacol. and Toxicology, Natl. Inst. of Pharmaceut. Educ. and Research, Kolkata, Kolkata, India

Abstract: Pharmacological modulation of SIRT3 ameliorates the type 2 diabetes associated cognitive impairment by upregulating hippocampal neurogenesis through Wnt 3a/β-catenin pathway Dibya Sundar Padhy*, Sugato Banerjee Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER)-Kolkata, 700054, India *Presenting Author: dibyasundarpadhy@gmail.com Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that increases the prevalence of cognitive impairment in the geriatric population. Hippocampal neurogenesis and synaptic plasticity are the primary cognitive reserve feeder mechanisms that are compromised in the diabetic brain. Sirtuin3 (SIRT3), a key mitochondrial NAD⁺-dependent deacetylase, is critically responsible for mitochondrial functional homeostasis and is highly associated with neuropathology. However, the role of SIRT3 in regulating hippocampal neurogenesis remains elusive. Methods: In the present study, we investigated the role of SIRT3 regulating hippocampal neurogenesis using trilobatin, a SIRT3 activator, in vivo and in vitro models of T2DM. Sprague-Dawley rats were administered with high-fat diet (HFD) and a single dose (35 mg/kg) of streptozotocin (STZ) for the T2DM induction. Trilobatin (10, 20 and 40 mg/kg) was administered orally for 28 days. Cognitive functions were evaluated by performing neurobehavioural assessments, such as spontaneous alternation test, novel object recognition test, and passive avoidance test. On the 15th week, rats were euthanised, and the hippocampus was isolated for biochemical and molecular analysis. For cellular studies, N2A cells were exposed to high glucose and trilobatin. Results: SIRT3 expression was significantly reduced in the hippocampus of diabetic rats and high glucose-exposed N2A cells. SIRT3 downregulation decreases the hippocampal neurogenesis by suppressing the Wnt 3a/ β-catenin pathway in HFD+STZ treated animals. Four weeks of trilobatin administration improved the hippocampal neurogenesis by modulating the SIRT3-mediated mitochondrial biogenesis and dynamics in the hippocampus of T2DM rats. It also sensitises the hippocampal insulin receptors, enhances cerebral glucose uptake and improves cognitive functions. In high glucose-exposed N2A cells, trilobatin (25 and 50 μM) treatment halts the mitochondrial ROS production and restores the impaired mitochondrial health. Conclusion: Overexpressing SIRT3 attenuates the T2DM associated cognitive decline by enhancing the hippocampal neurogenesis in rats, as well as high glucose-treated N2A cells via Wnt 3a/ β-catenin signalling modulation.

Disclosures: D.S. Padhy: None. S. Banerjee: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.06/KK13

Topic: I.08. Learning and Memory

Support: SECIHIT 800824
 SECIHIT 626561
 SECIHIT 1079765

Title: Repeated administration of a subanesthetic dose of ketamine results in impaired motor and cognitive behavior and differential expression of hippocampal P2X1 and P2X7 receptors in adult mice

Authors: ***A. O. CUELLAR SANTOYO**¹, V. M. RUIZ-RODRÍGUEZ⁴, K. HERNANDEZ-BALDERAS², A. M. ESTRADA SANCHEZ³;
¹IPICYT, San Luis Potosi, Mexico; ²IPICYT, Mexico, San Luis Potosi, Mexico; ³División de Biología Mol., IPICYT, San Luis Potosi, Mexico; ⁴Biología Mol., Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico

Abstract: Ketamine hydrochloride serves multiple purposes, including its use as a general anesthetic, treatment for depression, and recreational drug. In studies involving rodents, ketamine is utilized as a model for schizophrenia. However, it is unclear whether age affects the behavioral response induced by repeated ketamine administration and if it modifies the expression levels of N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and purinergic receptors (P2X1, P2X4, P2X7). In the present study, we evaluated the effect of intraperitoneal administration of subanesthetic ketamine dose (30 mg/Kg) for fourteen days on young (35 days of age) and adult (76 days of age) mice on different behavioral tests. Nest-building behavior was evaluated during the fourteen-day treatment; short-term memory and social interaction tests were assessed twenty-four hours after the last administration of ketamine. Interestingly, only adult mice treated with ketamine showed impaired nest-building and novel object recognition. In the hippocampus, an area related to memory and cognition, ketamine administration showed no changes in the relative expression of GluN1, P2X4, and P2X7 while increasing GluA2 and P2X1 only in young mice. In contrast, when assessing the protein levels of P2X1 and P2X7 in the hippocampus following ketamine treatment, young mice exhibited a decrease in P2X1 levels while P2X7 levels increased. In contrast, adult mice showed the opposite pattern; P2X1 levels were higher, and P2X7 levels decreased. These results suggest that adult mice are more vulnerable to repeated ketamine administration than young mice and that a differential response of P2X1 and P2X7 might contribute to ketamine-induced behavioral changes.

Disclosures: A.O. Cuellar Santoyo: None. V.M. Ruiz-Rodríguez: None. K. Hernandez-Balderas: None. A.M. Estrada Sanchez: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.07/KK14

Topic: I.08. Learning and Memory

Title: The Role of Sodium-Glucose Cotransporter-2 Inhibitors in Alleviating Cognitive Impairment in Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis

Authors: *R. MAHAFDEH¹, B. MAHAFDAH²;

¹Clin. Pharm. and Therapeut., Fac. of Pharmacy, Jadara Univ., Irbid, Jordan; ²Fac. of Medicine, Yarmouk Univ., Irbid, Jordan

Abstract: Background: Type 2 diabetes mellitus (T2DM) is a recognized risk factor for cognitive impairment and dementia. The pathophysiology of diabetes-related cognitive dysfunction involves insulin resistance in the brain, neuroinflammation, oxidative stress, impaired cerebral glucose metabolism, and cerebrovascular damage. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), while primarily used for glycemic control, have shown emerging neuroprotective effects. **Objective:** This systematic review and meta-analysis aimed to assess the impact of SGLT2i on cognitive outcomes in patients with T2DM. **Methods:** Following PRISMA 2020 guidelines, literature searches were performed across PubMed, Embase, and Web of Science databases from 2017 to March 2024. Eligible studies included randomized controlled trials (RCTs) and cohort studies evaluating the effects of SGLT2i on cognitive outcomes in T2DM patients. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Risk of Bias 2 (ROB 2) tool for RCTs. Pooled estimates were calculated using a random-effects model. Risk ratios (RR) and hazard ratios (HR) were reported for dichotomous outcomes, and standardized mean differences (SMD) for continuous cognitive outcomes, and Heterogeneity was assessed using the I^2 statistic. **Results:** Seven cohort studies comprising a total of 331,908 participants reported a statistically significant reduction in overall dementia risk among SGLT2 inhibitor users (RR = 0.69; 95% CI: 0.54-0.88). Subgroup analysis within these studies indicated a 30% lower risk of vascular dementia and a 20% reduction in Alzheimer's disease incidence in patients treated with SGLT2 inhibitors. Additionally, three randomized controlled trials (N = 182) demonstrated a modest but statistically significant improvement in cognitive performance (SMD = 0.44; 95% CI: 0.05-0.58; $I^2 = 47\%$), particularly in patients with mild cognitive impairment. These findings suggest a potential cognitive benefit associated with SGLT2i use in both observational and interventional settings. **Conclusion:** Our findings support the possible role of SGLT2 inhibitors as adjunctive therapy for cognitive decline in patients with type 2 diabetes. While these agents appear to offer neuroprotective benefits, the underlying mechanisms remain incompletely understood. This study highlights the need for further mechanistic investigations and large-scale, long-term randomized controlled trials to validate and clarify the cognitive benefits of SGLT2 inhibitors in this population.

Disclosures: R. Mahafdeh: None. B. Mahafdah: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.08/KK15

Topic: I.08. Learning and Memory

Support: GACR 23-05540S
EXREGMED CZ.02.01.01/00/22_008/0004562

Title: Perineuronal net modification via oral perineuronal net inhibitor improve memory in P301S mice

Authors: N. MARTINEZ VAREA¹, J. W. FAWCETT^{2,1}, *P. JENDELOVA¹, J. C. KWOK^{3,1};
¹Inst. of Exptl. Med. CAS, Prague, Czech Republic; ²Cambridge Univ., Cambridge, United Kingdom; ³Univ. of Leeds, Leeds, United Kingdom

Abstract: Alzheimer's disease (AD) is a progressive and debilitating disorder primarily characterized by memory loss, with significant motor impairments also being common. Enhancing neuroplasticity has emerged as a promising strategy to mitigate age-related dysfunction, and interventions such as chondroitinase ABC (ChABC) or antibody-based therapies for plasticity enhancement have shown preclinical efficacy; however, these approaches often lack translational potential. We previously demonstrated that oral administration of 4-methylumbelliferone (4Mu) could down-regulate chondroitin sulfates in the perineuronal nets (PNNs) and enhance memory performance in aged rodents. In the present study, we extend this work by evaluating whether 4Mu can also ameliorate cognitive impairments in a tauopathy model of AD. P301S tauopathy mice (n=11) received oral 4Mu or placebo treatment for 1 month followed by a 2-weeks washout period. Novel Object Recognition (NOR) tests were performed before and after 4Mu treatment, and after the washout. Histological analyses involved immunohistochemistry to quantify PNNs (WFA), tau aggregates (AT8) and neuroinflammatory markers (Iba1). Oral administration of 4Mu effectively reduced PNNs in the brain and spinal cord of P301S mice, as demonstrated by significant decreases in WFA signal intensity and area around PNN neurons. Behavioral analyses revealed that 4Mu treatment markedly improved cognitive performance, as evidenced by sustained enhancement in NOR tests at 3, 24, and 48 hours post-exposure compared to placebo treatment. The improvement in memory was sustained even after the washout period. Synaptic staining is on-going. Collectively, these findings suggest that oral 4Mu holds promise for ameliorating cognitive deficits in AD through modulation of neuroplasticity and neuroinflammation.

Disclosures: N. Martinez Varea: None. J.W. Fawcett: None. P. Jendelova: None. J.C. Kwok: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.09/KK16

Topic: I.08. Learning and Memory

Title: Receptor-specific modulation of fear extinction by 5-HT2A antagonists

Authors: *A. TYULMENKOVA¹, R. W. STACKMAN, Jr.²;

¹Biol., Florida Atlantic Univ., Jupiter, FL; ²Dept. of Psychology, Florida Atlantic Univ., Boca Raton, FL

Abstract: Understanding how neuromodulator systems influence fear extinction is essential for uncovering the neural mechanisms that support adaptive learning and for identifying novel therapeutic targets for trauma-related disorders. Among these systems, the serotonin 2A receptor (5-HT_{2A}R) has emerged as a key modulator of cortical excitability, emotional processing, and synaptic plasticity. Receptor-level investigations are particularly informative, as they allow for the dissection of molecular contributions to extinction dynamics across brain circuits. Here, we examined the role of serotonergic signaling in extinction learning in mice by comparing the effects of MDL 11,939, a 5-HT_{2A/2C} antagonist, and MDL 100,907, a highly selective 5-HT_{2A} receptor antagonist. Drug-free adult C57BL/6J mice underwent Pavlovian delay fear conditioning comprising 3 pairings of a tone CS with a 0.5 mA footshock in Context A. In **Exp't 1a (Acute)**, mice received either vehicle (5% DMSO) or MDL 11,939 (0.5 mg/kg or 1.0 mg/kg) 30 min prior to extinction day 1. In **Exp't 1b (Repeated Dose)**, the same treatments were administered on extinction days 1 and 2, with a final extinction session conducted 72 hr later in both experiments. In **Exp't 2 (Repeated Dose)**, mice were administered vehicle or MDL 100,907 (0.01 mg/kg or 0.03 mg/kg) on extinction days 1 and 2, with the final session on day 3. Extinction sessions consisted of 20 non-reinforced CS presentations with a 5-s ISI in Context B, distinct from the conditioning environment. Behavioral analyses revealed that MDL 11,939 significantly delayed extinction learning in both the acute and repeated-dose experiments. The 1.0 mg/kg dose significantly increased the number of trials required to reach extinction criteria, while the 0.5 mg/kg dose did not produce a significant effect. In contrast, MDL 100,907 had no impact on extinction performance at either dose. These findings suggest that the extinction impairments observed with MDL 11,939 are likely attributable to its broader pharmacological profile, potentially implicating 5-HT_{2C} receptor antagonism or off-target effects. The lack of behavioral disruption following selective 5-HT_{2A} receptor blockade with MDL 100,907 highlights the importance of receptor specificity in serotonergic modulation of fear extinction. Ongoing studies using region-specific intracranial drug delivery to the infralimbic cortex and basolateral amygdala aim to further localize these effects and clarify the circuit-level mechanisms involved.

Disclosures: A. Tyulmenkova: None. R.W. Stackman: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.10/KK17

Topic: I.08. Learning and Memory

Support: R01NS128123
R01MH122414

, a UWM Distinguished Dissertator Fellowship
a Support for Undergraduate Research Fellow award from the UWM
Office of Undergraduate Research

Title: Examining a role for 17 β -estradiol-induced regulation of ubiquitin proteasome system activity at hippocampal synapses following object training in ovariectomized female mice.

Authors: *P. MOHAMMADI¹, S. B. BEAMISH², T. J. JAROME³, K. M. FRICK²;
¹UWM, Milwaukee, WI; ²Psychology and Brain, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; ³Virginia Tech., Blacksburg, VA

Abstract: 17 β -estradiol (E2) enhances hippocampal function and long-term memory formation, but the molecular mechanisms remain unclear. E2 regulates hippocampus-dependent memory by activating cell-signaling cascades in the dorsal hippocampus (DH) to promote the synthesis of proteins that support structural changes at DH synapses. However, this work has overlooked protein degradation by the ubiquitin proteasome system (UPS). Our data indicate proteasome activity is necessary for E2 to enhance hippocampus-dependent spatial and object recognition memory consolidation in ovariectomized (OVX) female mice. Although these findings suggest E2 requires UPS-mediated protein degradation to enhance hippocampal memory, it is unclear when UPS-mediated protein degradation occurs and whether post-training E2 potentiates training-induced effects on UPS activity. Thus, this work examined the extent to which E2 regulates training-induced UPS activity at DH synapses in OVX mice. Adult female C57BL/6/J mice were bilaterally OVXed, implanted with bilateral guide cannulae targeting the DH, and then assigned to homecage+vehicle, train+vehicle, or train+E2 groups. Trained mice explored two identical objects in an open field for 30 s. After training, mice received a bilateral DH infusion of vehicle or E2 and DH tissue was collected 5 min, 1 h, and 4 h later. These timepoints represent peak (5 min, 4 h) and trough (1 h) periods of protein synthesis and protein degradation during consolidation. Synaptic fractions were analyzed for UPS-mediated degradation: 1) K48 polyubiquitination, representing protein tagging, 2) RPT6 phosphorylation, representing proteasome state, and 3) 20S proteasomal activity, representing proteasome catalysis. We find that trained vehicle-treated mice show decreased proteasome activity at 1 h, which is reinstated at 4 h. However, post-training DH infusion of E2 prevents this reinstatement at 4 h, suggesting E2 decreases overall proteasomal protein degradation at DH synapses 4 h following object training. Furthermore, E2 increases K48 polyubiquitination in DH cytoplasm at 4 h, suggesting reduced proteasome activity leads to accumulation of K48-tagged proteins. Ongoing work is examining the identity and number of proteins spared from degradation at 4 h via mass spectrometry.

Disclosures: P. Mohammadi: None. S.B. Beamish: None. T.J. Jarome: None. K.M. Frick: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.11/KK18

Topic: I.08. Learning and Memory

Support: AK0551472297-873000-191100NIH Rudolph R35 MIRA ends 2/28/2029

Title: Chronic Intermittent Propofol Reverses Cognitive Decline in a Model for Hippocampal Aging via $\alpha 5$ -GABA_A Receptors

Authors: ***R. NAGARAJAN**¹, J. LYU², M. KAMBALI¹, M. WANG², R. A. PEARCE³, U. RUDOLPH^{1,4};

¹Univ. of Illinois at Urbana-Champaign, Urbana, IL; ²Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Urbana, IL; ³Anesthesiol., Univ. of Wisconsin, Madison, WI; ⁴Carl R. Woese Inst. for Genomic Biology, Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Advancing age is linked to progressive cognitive decline. One contributing factor is the reduction of somatostatin-positive (Sst⁺) GABAergic interneurons in the dentate hilus of the hippocampus - a region essential for learning and memory. We previously demonstrated that selective ablation of Sst⁺ interneurons induces cognitive deficits, thereby creating a pseudo-aged mouse model for hippocampal aging. Chronic intermittent administration of propofol has been shown to have neuroprotective effects in aged and Alzheimer's disease mouse models, yet the mechanisms underlying its sustained action remain unclear. In this study, we investigated the non-canonical, sustained effects of chronic intermittent propofol (CIP) in young mice with Sst⁺ interneuron ablation. Male and female Sst-IRES-Cre mice (3-4 months old) and Sst-IRES-Cre/ $\alpha 5$ -GABA_A receptor global knockout ($\alpha 5$ KO) mice were used. Pseudo-aged mice were generated via bilateral injection of AAV5-EF1 α -mCherry-flex-dtA into the dentate hilus, while control mice received AAV5-EF1 α -mCherry. Animals were treated with CIP (75 mg/kg, i.p.) or vehicle (Intralipid®) every fifth day throughout the experimental period. Cognitive functions were assessed using a battery of behavioral tests. In pseudo-aged mice, CIP treatment significantly improved working memory (Y-maze), recognition memory (novel object recognition), non-declarative associative memory (trace fear conditioning), and spatial learning and memory (Morris water maze). These benefits of CIP were absent in $\alpha 5$ KO mice, suggesting that CIP's sustained effects are mediated by $\alpha 5$ -GABA_A receptors. In summary, chronic intermittent propofol reverses cognitive dysfunction in a model for hippocampal aging through $\alpha 5$ -GABA_A receptor-dependent mechanisms. Enhancing the function or expression of $\alpha 5$ -GABA_A receptors may represent a promising therapeutic strategy to combat age-related cognitive decline.

Disclosures: **R. Nagarajan:** None. **J. Lyu:** None. **M. Kambali:** None. **M. Wang:** None. **R.A. Pearce:** None. **U. Rudolph:** None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.12/KK19

Topic: I.08. Learning and Memory

Support: SECITHI 626561
SECITHI 800824
SECITHI 1241696

Title: Sex-dependent alterations induced by a subanesthetic dose of ketamine occur alongside changes in the Mouse ID associated 1 (MIDA1) protein

Authors: *A. B. VARGAS ANTILLÓN¹, A. O. CUELLAR SANTOYO³, O. RANGEL PEREZ², V. M. RUIZ-RODRÍGUEZ⁵, O. A. PATRÓN SOBERANO⁶, A. M. ESTRADA SANCHEZ⁴;

¹Biología Molecular, ²Biología Mol., Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico; ³Biología Mol., ⁴División de Biología Mol., IPICYT, San Luis Potosí, Mexico; ⁵Biología Mol., Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico; ⁶Mol. Biol., Inst. Potosino de Investigación Científica y Tecnológica A.C., San Luis Potosí, Mexico

Abstract: Ketamine is a non-competitive inhibitor of the glutamatergic N-methyl-D-aspartate (NMDA) receptors, commonly used as an anesthetic, a treatment for depression, and as a recreational drug. Previously, we observed a sex-dependent effect of ketamine on certain cognitive behaviors in mice. These changes may relate to the impact of ketamine on the expression of epigenetic regulators and the upregulation of chaperone protein levels. However, it remains unclear whether the Mouse ID associated 1 (MIDA1) protein, located in the nucleus and cytoplasm and known for its transcriptional, epigenetic, and chaperone activity, is influenced by this anesthetic. Therefore, in this study, we evaluated the effects of daily ketamine administration (14 consecutive days at 30 mg/kg) on behaviors related to the hippocampus and motor cortex, and whether ketamine modified the relative expression and protein levels of MIDA1. Our results show that ketamine administration did not alter the transcript levels of MIDA1 in the hippocampus. However, the motor cortex of male mice treated with ketamine displayed a significant reduction in MIDA1. Next, we assessed whether ketamine treatment affects the cellular distribution of MIDA1 in the motor cortex using an immunofluorescence assay. The total fluorescence intensity increased in the motor cortex of males treated with ketamine. Yet, when we specifically evaluated the fluorescence of pyramidal neurons, we found that in females, these neurons exhibited a significant increase in MIDA1. Overall, these findings suggest that chronic NMDA receptor inhibition via ketamine selectively disrupts cognitive and social behaviors, likely involving hippocampal and cortical circuits, with males being more susceptible. Additionally, the described differential effects may be partly associated with the target genes of MIDA1, warranting further research.

Disclosures: A.B. Vargas Antillón: None. A.O. Cuellar Santoyo: None. O. Rangel Perez: None. V.M. Ruiz-Rodríguez: None. O.A. Patrón Soberano: None. A.M. Estrada Sanchez: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.13/KK20

Topic: I.08. Learning and Memory

Support: ICMR Grant

Title: Blood-brain barrier-permeable hdac3 selective inhibitor sp108 ameliorates hippocampal-dependent cognitive dysfunction in mam-induced animal model of schizophrenia

Authors: *A. GHOSH¹, O. P. KULKARNI²;

¹Pharm., Birla Inst. of Technol. & Sciences, Pilani, Hyderabad Campus, Hyderabad, India;

²Pharm., Birla Inst. of Technol. & Sciences, Pilani, Hyderabad Campus, Hyderabad, India

Abstract: Schizophrenia is a complex neurodevelopmental disorder characterized by positive, negative, and cognitive symptoms. While DNA methylation changes are implicated, the role of histone deacetylase 3 (HDAC3) remains underexplored in psychosis. Given its involvement in neurodevelopment and synaptic plasticity, HDAC3 may serve as a critical modulator of schizophrenia-associated multiple paradigms. We induced schizophrenia-like phenotypes by administering methylazoxymethanol acetate (MAM; 20 mg/kg) to pregnant rats on gestational day 17. Behavioral paradigms assessing positive (pre-pulse inhibition, MK801-induced hyperlocomotion), negative (social interaction test), and cognitive (active avoidance task) symptoms in the next generation adult males were employed. HDAC3 expression and enzymatic activity were evaluated using immunoblotting and confocal microscopy. Postnatal treatment with a selective, brain-permeable HDAC3 inhibitor SP108 (25 mg/kg, i.p., 3 weeks) was administered, and behavioral and molecular outcomes were reassessed. MAM-exposed offspring displayed hallmark schizophrenia-like behaviors, including impaired sensorimotor gating, heightened MK801-induced hyperlocomotion, reduced social interaction, and significant deficits in active avoidance learning. HDAC3 expression and enzymatic activity were markedly upregulated in the hippocampus of MAM-exposed rats compared to controls. SP108 ameliorated deficits in pre-pulse inhibition and increased the % avoidance in the active avoidance task. SP108 elevated acetylated histone (H3K9ac) in CA2/3 regions and elevated BDNF-PSD95-Synapsin-1 in the isolated hippocampal tissues. These findings demonstrate that SP108-mediated HDAC3 inhibition improves hippocampal-dependent cognitive function in schizophrenia, underscoring its potential as a targeted therapeutic approach.

Disclosures: A. Ghosh: None. O.P. Kulkarni: None.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.14/KK21

Topic: I.08. Learning and Memory

Support: UG3/UH3NS127386

Title: Preclinical lead EP2 antagonist attenuates cognitive impairments and cumulative seizure burden in status epilepticus mice

Authors: S. POURKHODADAD¹, P. HEMAN BOZADAS⁶, R. J. DINGLELINE⁷, W. WANG⁸, N. H. VARVEL², V. RAWAT³, H. XING⁴, A. ROJAS, Sr.⁹, *T. GANESH⁵;

¹Emory Univ., Decatur, GA; ²Pharmacol., ³Pharmacol. and Chem. Biol., ⁴Dept. of Pharmacol. and Chem. Biol., ⁵Emory Univ., Atlanta, GA; ⁶Pharmacol. and Chem. Biology, Sch. of Medicine, Emory Univ., Atlanta, GA; ⁷Dept Pharmacol, Emory Univ. Sch. Med., Atlanta, GA; ⁸Emory SOM, Atlanta, GA; ⁹pharmacology, Emory Univ. (SOM), Atlanta, GA

Abstract: EP2 receptors activated by endogenous PGE2 promote neuroinflammation in several acute and chronic central nervous system diseases, including status epilepticus (SE), traumatic brain injury (TBI), and Alzheimer's disease (AD). Neuroinflammation is strongly associated with breakdown of blood-brain-barrier and neurodegeneration and ensuing cognitive deficits and emergence of chronic spontaneous (epileptic) seizures in models of status epilepticus and TBI. Our laboratory has been developing selective small-molecule antagonists for EP2 receptors to determine the functional role in neuropathology and behavioral deficits in SE, TBI, and AD models, with the ultimate goal of developing EP2 antagonists for clinical use. Lead-optimization on our previous EP2 antagonist BPN-30343 with structure activity relationship (SAR) studies through nearly 250 derivatives identified a novel lead BPN37440, which possessed excellent EP2 potency, selectivity against other prostanoid receptors (EP4, DP1 and IP and competitive binding mechanism to EP2 using the functional cAMP assay (Schild potency 5.6 nM with Schild slope = ~1). Moreover, this compound also demonstrated anti-inflammatory actions in the BV2-hEP2 cellular model, and suitable in vitro ADME and in vivo PK properties to be useful for advancement to preclinical studies. A fleeting exposure of BPN-37440 (3 injections within first 24 hours) after SE onset in mice attenuated microgliosis in Amygdala, neocortex, and hippocampus CA3 region (determined by histology) 4 days following recovery from SE, and spatial working memory deficits (measured through Y-maze, Novel Object Recognition test, and Barnes Maze) 1-1.5 months after recovered from SE. A separate cohort of mice was treated similarly with an EP2 antagonist, which attenuated the cumulative seizure burden (examined through cortical EEG recording), 3-4 months after recovery from SE. The results reinforce the notion that neuroinflammation promoted by EP2 activation exacerbates neuroinflammatory pathology and ensuing behavioral deficits and the emergence of chronic spontaneous seizures after SE in mice.

Disclosures: S. pourkhodadad: None. P. Heman Bozadas: None. R.J. Dingleline: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I am an inventor in a patent application associated with this abstract. W. Wang: None. N.H. Varvel: None. V. Rawat: None. H. Xing: None. A. Rojas: None. T. Ganesh: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I am a listed inventor in a patent application related to this work.

Poster

PSTR046: Pharmacology of Learning

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR046.15/KK22

Topic: A.07. Development of Neural Systems

Support: JUST-Deanship of Research

Title: Sucrose Administration and Noxious Stimulation during The First Week of Rat Pups' Lives: Long-Term Behavioral and Developmental Implications

Authors: M. ALSHANNAG, R. BANI ESSA, S. NUSAIR, ***K. NUSEIR**;
Clin. Pharm., Jordan Univ. of Sci. and Technol., Irbid, Jordan

Abstract: Up to 90% of premature babies delivered prematurely are admitted to the Neonatal Intensive Care Unit (NICU). During their stay, they are subjected to numerous painful diagnostic and therapeutic procedures without adequate analgesia. Heel lance is a widely used blood sampling technique, amounting up to 21 heel pricks daily. The undermanagement of pain in this vulnerable population was always attributed to their immature thalmo-cortical connections. However, many studies have shown that they do experience pain; and this pain is associated with several neurostructural, neurobehavioral, and pain processing changes. Due to their safety profile, non-pharmacological analgesic approaches like oral sucrose have gained attention. Sucrose was found to induce analgesia and reduce pain in infants through the activation of the endogenous opioid system. This work investigated the potential role of sucrose in mitigating the long-lasting effect of noxious stimulation during the first week of life in rat's pups as it matches the age of a premature human, considering sex differences. Noxious stimulation was induced in a way mimicking the heel lance process using a tiny needle inserted and removed quickly into the rat pups' paws four times a day for 7 days. The pups were assigned to receive either no treatment (N), sucrose (SN) or water (WN) before noxious stimulation. Tactile (T) stimulation was carried out by touching the paws with a cotton swab. Several behavioral tests were then conducted at different age points. Rats were decapitated at 10 weeks of age, blood samples were collected to assess the oxidative stress state and the corticosterone levels, and hippocampus was dissected to measure the levels of brain-derived neurotrophic factor (BDNF). Preliminary results showed sex-specific variations in terms of responding to different stressors, female rats appeared to be more vulnerable to long-term consequences. Noxious stimulation during infancy lowered thermal pain threshold, increased anxiety-like behaviors later in adulthood, and increased corticosterone levels in female rats. Sucrose showed both protective and paradoxical effects. It improved the noxious stimulation-induced thermal pain hypersensitivity at 8 weeks of age but increased it at 4 weeks of age; decreased the resulted hyperactivity of female rats in the open field test and enhanced the BDNF levels in male rats. In conclusion, our findings illustrate that noxious stimulation during infancy increases thermal sensitivity, alters different behavioral responses in adulthood, and affects the corticosterone levels; sucrose treatment producing mixed effects, all in a sex-specific manner.

Disclosures: M. Alshannag: None. R. Bani Essa: None. S. Nusair: None. K. Nuseir: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.01/LL1

Topic: I.03. Decision Making

Support: NIH Grant R01MH129582

Title: A state-representation-independent statistical test of the dopamine reward prediction error hypothesis

Authors: ***L. KUSMIERZ**¹, J. DISANTO², Y. YOON³, C. KIRST⁴, V. K. NAMBOODIRI⁵, S. MIHALAS⁶;

¹Allen Inst., Seattle, WA; ²Univ. of California, San Francisco, San Francisco, CA; ³Neurol., UCSF, San Francisco, CA; ⁴Anat., The Rockefeller Univ., San Francisco, CA; ⁵Neurol., Univ. of California San Francisco, San Francisco, CA; ⁶Studio D3, Allen Inst. For Brain Sci., Seattle, WA

Abstract: Neuromodulators like dopamine play a critical role in learning and decision-making by shaping neural computations and plasticity. A leading hypothesis in the field is that midbrain dopamine neurons represent reward prediction errors (RPEs). However, this hypothesis is difficult to test as reward predictions depend on the experimentally inaccessible state representation used to encode the value. Moreover, different algorithmic instantiations of temporal-difference reinforcement learning (TDRL) yield different RPEs, and signals recorded from dopamine neurons may map to RPEs in a nonlinear way.

We propose an analytical method for testing the RPE hypothesis that does not require knowledge of the underlying state representation, the specific TDRL algorithm, or the monotonic nonlinearity mapping RPEs to observed dopamine signals. The method rests on two key assumptions: (a) dopamine encodes an error signal used to update value estimates and/or policy, and (b) value estimates eventually reach a steady state. Under these assumptions, the steady-state error signals, stratified by conditioning on past sensory experiences, should all have zero mean, and the conditional empirical distribution functions of the corresponding (monotonically transformed) observations must intersect.

We validated our method using simulated data with known ground truth, demonstrating its ability to distinguish RPE from non-RPE signals in actor-critic, SARSA, and Q-learning models. We then applied the method to experimental fiber photometry data collected from mice performing a novel Markov chain Pavlovian conditioning task. Following the initial learning phase, most animals exhibited stable behavior consistent with having learned state values. However, our method indicated that phasic dopamine did not correspond to a steady-state error signal, contradicting the RPE dopamine hypothesis.

Disclosures: **L. Kusmierz:** None. **J. DiSanto:** None. **Y. Yoon:** None. **C. Kirst:** None. **V.K. Namboodiri:** None. **S. Mihalas:** None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.02/LL2

Topic: I.03. Decision Making

Support: F30MH136699
R01MH118369

Title: Roles of GABAergic Interneurons in the Dorsal Striatum in Value-Based Decision-Making

Authors: *E. ILIAKIS¹, A. RAMIREZ⁶, J. MUHSINOV², J. GALANAUGH³, J. WOOLLEY⁴, I. LINARES-GARCIA⁷, K. CHOI⁹, S. M. FERRIGNO⁵, E. DIAZ-HERNANDEZ¹⁰, W. TU¹, E. N. HOLLY⁸, D. J. MARGOLIS¹¹, M. V. FUCCILLO³;

²Sch. of Arts and Sci., ³Neurosci., ⁴Sch. of Med., ⁵Neurosci. Grad. Group, ¹Univ. of Pennsylvania, Philadelphia, PA; ⁶Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; ⁷Dept. of Neuroscience, Sch. of Med., ⁸Neurosci., Rutgers University-Newark, Newark, NJ; ⁹Neurosci., Hallym Univ., Chuncheon, Korea, Republic of; ¹⁰Neurosci., Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA; ¹¹Cell Biol. & Neurosci., Rutgers, The State Univ. of New Jersey, Piscataway, NJ

Abstract: Value-based decision-making aims to maximize rewards in changing environments. Abnormalities in value-based decision-making are a feature of a range of neuropsychiatric diseases and are functionally impairing. The dorsal striatum (DS) is critical for the execution of value-based decision-making. Within the DS, the role of sparse GABAergic interneurons in behavior is of increasing interest. Tyrosine hydroxylase-positive (TH+) interneurons (THINs) are necessary for maintaining goal-directed strategies, while somatostatin-positive (SST+) low-threshold spiking interneurons (LTSIs) exhibit novel reward-related activity that decays throughout operant learning. However, the role of DS THINs and LTSIs in value-based decision-making is not known. To study their role in decision making, we have developed a head-fixed joystick-based two-alternative forced choice behavioral paradigm in mice that assays the effect of varying relative reward values and reward probabilities on value-based choice and motor vigor. Fiber photometry recordings of these interneuron subtypes suggest key roles of their phasic activity in execution of value-based choice and modulation of motor vigor. Pilot optogenetic and chemogenetic manipulations hint at causal roles in decision-making. Simultaneous out-of-task manipulation of both interneuron subtypes and recordings of genetically identified striatal neuronal subpopulations suggest robust effects of interneuron manipulations on local microcircuitry dynamics. These findings contribute to a growing evidence base on the role of striatal microcircuitry in striatal function and behavior, with potential translational relevance suggested by evidence implicating striatal interneurons in a range of neuropsychiatric disease presentations.

Disclosures: E. Iliakis: None. A. Ramirez: None. J. Muhsinov: None. J. Galanaugh: None. J. Woolley: None. I. Linares-Garcia: None. K. Choi: None. S.M. Ferrigno: None. E. Diaz-Hernandez: None. W. Tu: None. E.N. Holly: None. D.J. Margolis: None. M.V. Fuccillo: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.03/LL3

Topic: I.03. Decision Making

Support: NSTC Grant 113-2628-B-002-002
NSTC Grant 112-2628-B-002-011
NSTC Grant 111-2628-B-002-036
NHRI Grant NHRI-EX113-11303NI
NHRI Grant NHRI-EX114-11303NI
NTUMC Grant 110C101-011
NTUH Grant 113-E0001

Title: Optogenetic duality: firing rate changes and neuronal synchrony modulation show differential effects on cerebellar reward coding

Authors: L.-Y. LU¹, P. CHEN², *M.-K. PAN³;

¹Inst. of Biomed. Sci., Academia Sinica, Taipei, Taiwan; ²Grad. Inst. of Pharmacology, Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan; ³Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

Abstract: Optogenetics offers unparalleled temporal precision and cell-type specificity, enabling direct interrogation of causal links between neuronal activity and behavior. Traditionally, optogenetic effects have been attributed primarily to changes in firing rate. However, in awake-behaving animals, optogenetic manipulations can induce both firing-rate and neuronal synchrony changes. Whether these two dimensions produce distinct behavioral consequences remains unclear. To address this, we examined reward coding in the deep cerebellar nucleus (DCN) to ventral tegmental area (VTA) pathway during a two-choice foraging task. We found that reward delivery was encoded by brief (as short as 2 ms), synchronous silencing of DCN population neurons, which in turn evoked rebound phasic firing in the VTA—a known correlate of reward signaling. Remarkably, both optogenetic excitation and inhibition of DCN-to-VTA projections biased choices toward reward and generated VTA phasic responses, despite producing opposing effects on DCN firing rates. To resolve this paradox, we analyzed DCN activity in terms of both firing rate and synchrony. While optogenetic excitation and inhibition showed opposite effects in neuronal firing rates, both manipulations enhanced synchrony, defined as the proportion of neurons showing the same direction of firing-rate change. To test the necessity of synchrony, we applied hyperpolarizing direct current to DCN neurons, which increased neuronal firing rates but suppressed synchrony. This intervention abolished reward-related behaviors and prolonged

decision time, indicating that synchrony, but not firing rate, was critical for reward coding. Computational modeling further supported this conclusion. Asynchronous increases in DCN firing led to gradual VTA activation without phasic responses, mimicking the effect of direct current. In contrast, synchronous activation or silencing of DCN neurons, mimicking the corresponding optogenetic effects, elicited robust VTA phasic responses. Importantly, even without changing the firing rates of individual neurons, aligning a single action potential across the DCN population was sufficient to trigger VTA phasic firing. In summary, our combined electrophysiological, behavioral, perturbational, and modeling results reveal that optogenetics works in two independent domains: the rate-coding and neuronal synchrony domains. In cerebellar reward coding, the optogenetic effect is purely attributed to neuronal synchrony but not firing rate manipulation. These findings emphasize the need to consider synchrony as a distinct mechanism in interpreting optogenetic effects on behavior.

Disclosures: L. Lu: None. P. Chen: None. M. Pan: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.04/LL4

Topic: I.03. Decision Making

Support: UK Medical Research Council Grant UKDRI-Edin007

Title: Medial prefrontal cortex leads and enhances functional connectivity with dorsomedial striatum in need for change during flexible behavior

Authors: *M. LIU^{1,2}, W. XU¹, P. SERIES¹, J. GAN^{1,2};

¹Univ. of Edinburgh, Edinburgh, United Kingdom; ²UK Dementia Res. Inst. at the Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Being cognitively flexible is vital for an individual's survival, and its deficit is a key symptom in many psychiatric conditions and neurodegenerative diseases. While both the medial prefrontal cortex (mPFC) and dorsomedial striatum (DMS) are essential to cognitive flexibility, their specific roles—particularly which region first detects and encodes environmental changes—remain debated. Employing head-restrained mice performing an action-outcome history-based choice task, we discover that a large fraction of medial prefrontal cortex (mPFC) and dorsomedial striatum (DMS) neurons represent the difference in reward history of available options, a key decision variable that prescribes advantageous choices. Importantly, mPFC tracks the change of this variable earlier and faster than DMS, and temporally targeted optogenetic interference with the variable's representation in mPFC impairs decision-making. Moreover, functional connectivity between mPFC and DMS increases with reducing overall reward proportion. Our results support a framework in which the prefrontal cortex is the first responder to the change of inferred environmental variables in the prefrontostriatal circuitry. It strengthens

communication with striatum to bias behavioral engagement towards a beneficial strategy in flexible behavior.

Disclosures: M. Liu: None. W. Xu: None. P. Series: None. J. Gan: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.05/LL5

Topic: I.03. Decision Making

Support: NHMRC GNT203346
NHMRC GNT2028533

Title: Modelling compulsive-like actions in rats and mice: mimicking the neuropathological features of compulsivity and developing punishment-resistant attentional capture

Authors: *L. A. BRADFIELD¹, O. SOEGYONO², M. D. KENDIG³, S. KILLCROSS⁴;
¹Univ. of Sydney, Sydney, Australia; ²Univ. of New South Wales, Sydney, Australia; ³Sch. of Life Sci., Univ. of New South Wales, Ultimo, Australia; ⁴Univ. of New South Wales, Randwick, Sydney, Australia

Abstract: Effective animal models are essential for identifying the brain and behavioural mechanisms of compulsive disorders, as well as how to treat them. Nevertheless, a broadly agreed-upon animal model of transdiagnostic compulsivity is lacking. To achieve better cross-species translatability, recent work in our laboratory has focused on back-translating behavioural tasks from humans to rodents, and simulating neuropathological features associated with compulsivity. In this study, we created a rodent version of the ‘value-modulated attentional capture’ task that, in humans, has been consistently shown to associate with and predict compulsivity across a range of mental health conditions, including obsessive-compulsive disorder, gambling disorder, and substance use disorder. In the first stage of this task, rats or mice were trained to sign-track to two levers, one associated with a low value reward (a single pellet) and another with a high value reward (3 pellets). Rodents were next trained to nose-poke an illuminated port on the opposite side of the operant chamber for pellets. In the final attentional capture stage, rodents were required to continue to nose-poke for reward whilst ignoring the levers which now functioned as distractors. In a replication of the pattern observed in humans, rodents failed to perform this target nose-poke response more often in the presence of the high value lever distractor relative to the low value distractor, indicating value-modulated attentional capture. Moreover, this result persisted despite conditioned taste aversion conditioning of the pellet outcome, even when that disliked outcome was delivered to ‘punish’ responding. In a second experiment we found that this effect was facilitated in rats who had had neuroinflammation induced in their nucleus accumbens core. Interestingly, it did so despite impairing the sign-tracking that the effect relies on. Together, these results demonstrate a new

way to model the compulsive-like phenomenon of attentional capture in rats and mice and highlight a facilitating role for striatal neuroinflammation in this process.

Disclosures: L.A. Bradfield: None. O. Soeggyono: None. M.D. Kendig: None. S. Killcross: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.06/LL6

Topic: I.03. Decision Making

Support: Simons Foundation SCGB Grant 542981

Title: The hippocampus encodes counterfactual scenarios during change-of-mind behavior

Authors: *S. GU^{1,2}, A. GILLESPIE³, C. LIU^{1,4}, R. NEVERS¹, L. M. FRANK⁵;

¹Univ. of California, San Francisco, San Francisco, CA; ²Univ. of California, Berkeley, Berkeley, CA; ³Biol. Structure, Univ. of Washington, Seattle, WA; ⁴Univ. of Chicago, Chicago, IL; ⁵Departments of Physiol. and Psychiatry, UC San Francisco, San Francisco, CA

Abstract: In understanding causal relationships, the ability to revise initial decision-making strategies and to try alternative solutions is thought to be fundamental [1, 2]. We devised an experimental paradigm in an arena consisting of a home arm, a central platform, and four choice arms. Rewards are delivered based on a hidden causal structure with two rules: the animal must return to the home arm after each visit to the reward port at the end of a choice arm, and rewards in a given choice arm (e.g. arm 4) only become available after the animal has obtained reward at a specific previous choice arm (e.g. arm 1). Thus, a correct sequence might be: home - 1 - home - 4 - home - 2 - home - 3 - home - 1. Rats learned to perform the correct sequence across 7-21 days and frequently exhibited change-of-mind behaviors where they entered a given choice arm and then reversed before visiting another arm and poking the reward port. These behaviors were often seen when animals were correcting for pre-existing biases in choice arm visit order. Change-of-mind trials resulted in higher reward rates than would have been obtained if the animals visited the reward port in the choice arm instead of reversing. These results suggest that the changes of mind are predominantly corrective. Previous research has linked counterfactual thinking to changes of mind [2, 3]. The hippocampus supports mental simulations, including counterfactuals, and we therefore examined activity in dorsal CA1 throughout learning. We found that, following the animal's decision to come to a stop and begin reversing during a change-of-mind, the hippocampus frequently expressed extended theta sequences that often contain spatial trajectories approaching the end of the initial choice arm the animal is moving away from, consistent with mental simulation of a counterfactual. We did not, however, observe sharp-wave ripple events during these periods, in contrast to a previous result in a fear conditioning study [4]. Altogether, our study documents behaviors and hippocampal neuronal

processes underlying the change of mind behavior as the rats learn a set of causal relationships. Our result adds to the previous observation that the hippocampal non-local representation during theta sequences interleaves current and counterfactual scenarios, which we hypothesize to be conducive to causal inference. [1] Stone, Caleb et al. (2022). On second thoughts: changes of mind in decision-making. [2] Pearl, J., & Mackenzie, D. (2019). The book of why. [3] Kruger, J., Wirtz, D., & Miller, D. T. (2005). Counterfactual thinking and the first instinct fallacy. [4] Wu, C. T., Haggerty, D., Kemere, C., and Ji. D. (2017). Hippocampal awake replay in fear memory retrieval.

Disclosures: S. Gu: None. A. Gillespie: None. R. Nevers: None. L.M. Frank: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.08/LL8

Topic: I.03. Decision Making

Title: Value computation of multi-item bundles in prefrontal cortex during economic decision-making

Authors: *Y. HUANG^{1,2}, R. ZHU^{1,2}, R. SU¹, W. ZHANG¹, C. REN¹, Z. ZHAO¹, T. YANG¹;

¹Inst. of Neuroscience, State Key Lab. of Brain Cognition and Brain-inspired Intelligence Technology, Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China; ²Univ. of Chinese Acad. of Sci., Beijing, China

Abstract: Economic decisions are based on the subjective value incorporating preference. Yet, how the brain computes the subjective value of an offer bundle consisting of multiple items with different reward types is not well understood. Here, we trained two macaque monkeys to choose between two bundles, each containing three items associated with one of the two kinds of juice. Single-unit activity was recorded from the orbitofrontal cortex (OFC) and ventrolateral prefrontal cortex (vLPFC). The monkeys made choices based on the combined subjective value of the offer bundles. Consistently, population activity in the OFC and vLPFC encoded the total subjective value of the chosen bundle. However, at the level of individual neurons, both the OFC and vLPFC neurons encoded the value of single items. Statistics on population revealed a salience-weighted pattern: higher-salience items recruited more neurons. In addition, some neurons in the OFC would switch from encoding the value of an item in the unchosen bundle to encoding the value of an item in the chosen bundle in the late period of the trial. Such transitions were rare among the vLPFC neurons: they consistently encoded the value of the same items throughout the trial. Finally, we found that separate neural subpopulations encoded values for the two types of juice. Together, these findings suggest that bundle value is not represented in individual neurons of the OFC and vLPFC, while the neural populations of these two regions collectively represent integrated bundle values through distributed salience-weighted encoding.

Disclosures: Y. Huang: None. R. Zhu: None. R. Su: None. W. Zhang: None. C. Ren: None. Z. Zhao: None. T. Yang: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.09/LL9

Topic: I.03. Decision Making

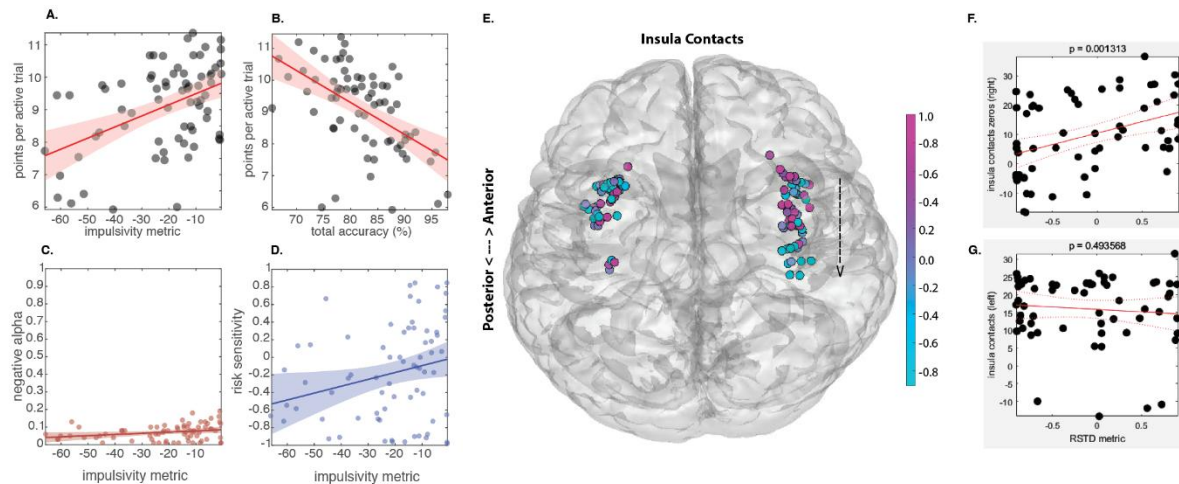
Support: NIH Grant R01MH128187

Title: An anatomical gradient of risk sensitivity in the human insula

Authors: *R. COWAN¹, T. S. DAVIS¹, B. KUNDU³, S. RAHIMPOUR², B. SHOFTY², J. D. ROLSTON⁴, T. H. MULLER⁵, S. W. KENNERLEY⁵, E. H. SMITH²;

²Neurosurg., ¹Univ. of Utah, Salt Lake City, UT; ³Neurosurg., Univ. of Missouri, Columbia, MO; ⁴Neurosurg., Brigham and Women's Hosp., Newton, MA; ⁵Univ. Col. London, London, United Kingdom

Abstract: Risk aversion can minimize losses, but also rewards, leading to maladaptive decision-making. If learning is dictated by better-than-expected outcomes, this indicates optimistic tendencies, correlating with risk-seeking, whereas learning from worse-than-expected outcomes indicates pessimistic tendencies, correlating with risk-aversion. Using intracranial recordings from 72 neurosurgical epilepsy patients, we examined behavioral and neural processes during a risky decision-making task: the Balloon Analogue Risk Task (BART). Overall, we observed a tradeoff between points awarded and accuracy that correlated with risk sensitivity (RS)—overall better task performance, measured by points gained, was tied to lower accuracy. We modeled behavior with standard and risk sensitive temporal difference (RSTD) learning models to estimate reward expectation and reward surprise (or prediction error; PE) during BART. An RSTD model derived RS metric—the ratio between the difference and the sum of negative and positive PEs—positively correlated with task-derived risk aversion ($p = 0.03$). To examine how participants' brains represented variations in risk aversion, (i.e., optimism or pessimism), we quantified how broadband high frequency (HFA: 70 - 150Hz) signals on each of the 5617 macroelectrode contacts encoded the best positive and negative learning rates from the RSTD model. RS PE and reward PE were encoded on >500 contacts, including nucleus accumbens and cingulate. Finally, we looked for anatomical organization of optimism and pessimism. Intriguingly, we observed an optimism gradient along the anterior-posterior dimension of the right insula ($t(59)=3.37$, $p=.001$), supporting prior fMRI work. Our findings reveal a novel feature of risk processing in the human brain suggesting the insula as an appropriate target for stimulation to modulate risk behavior, with clear implications for clinical and psychiatric populations. Moreover, this highlights the capability of the RSTD model to allow for dynamic observation of risk processing in the brain, beyond simple TD models.



Disclosures: R. Cowan: None. T.S. Davis: None. B. Kundu: None. S. Rahimpour: None. B. Shofty: None. J.D. Rolston: None. T.H. Muller: None. S.W. Kennerley: None. E.H. Smith: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.10/LL10

Topic: I.03. Decision Making

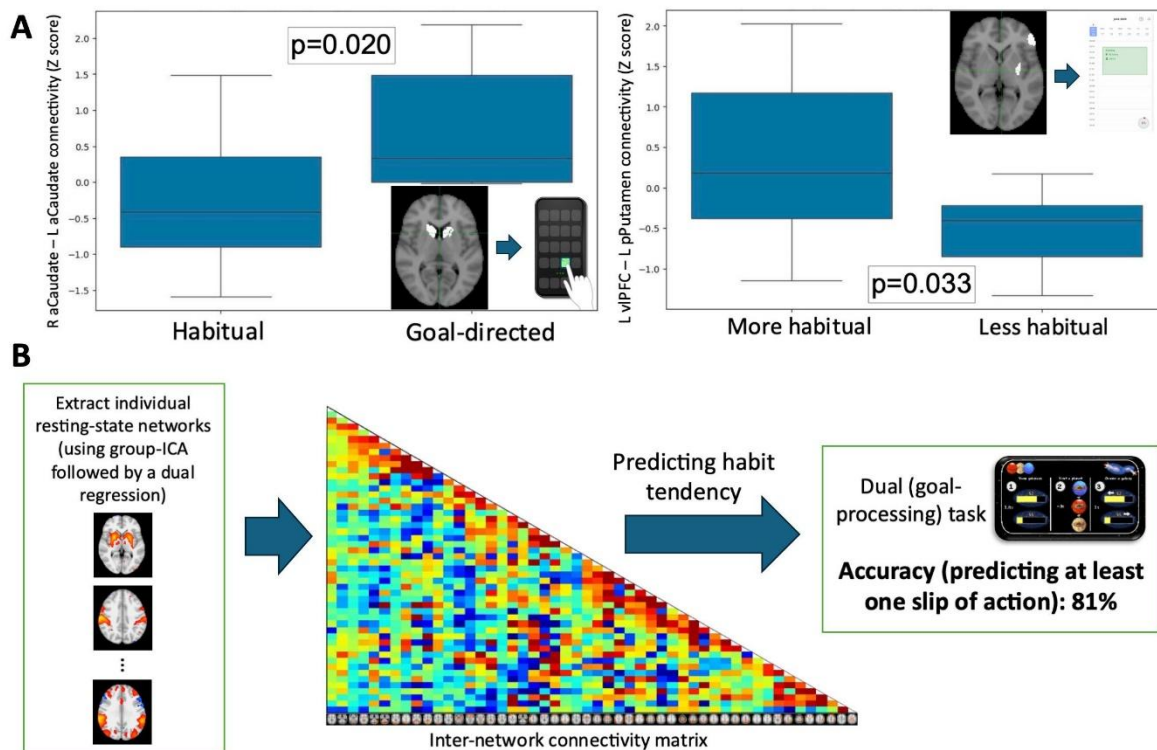
Support: T&C Chen Center for Social and Decision Neuroscience Shared Postdoctoral Fellow Award
Research was sponsored by the U.S. Army Research Office and accomplished under cooperative agreement W911NF-19-2-0026 for the Institute for Collaborative Biotechnologies

Title: Neural predictors of habit propensity: insights from real-world behavior and functional connectivity

Authors: *R. GERA¹, C. CAMERER¹, J. P. O'DOHERTY²;
¹Caltech, Pasadena, CA; ²California Inst. Technol., Pasadena, CA

Abstract: Habits play a crucial role in both adaptive and maladaptive behaviors, yet individuals vary widely in how they form and express them. Little is known about the neurobiological basis of these differences, particularly in real-life settings. Prior research implicated fronto-striatal circuits in habitual control, but findings are inconsistent, possibly due to reliance on laboratory-based tasks that may fail to capture the complexity of real-world habits. To address this gap, we developed a novel framework integrating active and passive measures to quantify real-world habits. Over 14 days, participants ($n=21$, 15 females, ages 19-54, mean = 28.8, SD = 7.35, data

collection is ongoing) completed daily activity reports, ecological momentary assessments, and continuous monitoring via smartphone and wearable sensors (e.g., GPS, phone use). A smartphone-based habit induction task captured the transition from goal-directed to habitual behavior, while a lab-based task measured habitual slips-of-action. Participants also underwent multimodal MRI scanning to examine neural correlates of habit propensity. We tested (for the first time) whether resting-state functional connectivity (rs-fMRI) in cortico-striatal circuits differs between habitual and non-habitual subgroups. Preliminary results suggest stronger bilateral caudate connectivity is associated with fewer habitual slips, while higher vIPFC-putamen connectivity correlates with greater real-life habit tendencies. To test whether habit propensity could be predicted from neural patterns, we trained a classifier on whole-brain functional connectivity, achieving 81% accuracy (cross-validated) in predicting habitual slips, suggesting habit propensity may be a stable neural trait shaped by distributed brain networks. Ongoing work aims to expand the sample and integrate structural connectivity (diffusion tensor imaging) to further understand and improve the prediction of habitual behavior.



Relating neural data to individual habit propensity (n=18-21). **A. left:** Bilateral caudate connectivity is significantly stronger for individuals who express no habitual responses in a habit induction app. **right:** Left vIPFC connectivity with the Left posterior putamen is significantly stronger in individuals who had greater tendency to habitual routines (formulated as STD of repeated daily activity starting times). **B)** Example pipeline and preliminary results of predicting habit propensity (measured as habitual slips-of-actions in a novel habit induction task) from the entire resting-state network connectivity. ICA: independent component analysis.

Disclosures: R. Gera: None. C. Camerer: None. J.P. O'Doherty: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.11/LL11

Topic: I.03. Decision Making

Support: NIMH R21MH120805

Title: Distinct computational markers of reward learning in anxiety and depression

Authors: *J.-H. LEE¹, C. GROSSMAN², J. D. FEUSNER³, R. TADAYON NEJAD⁴, S. OH⁵, J. COCKBURN⁶, W.-Y. AHN¹, J. P. O'DOHERTY²;

¹Dept. of Psychology, Seoul Natl. Univ., Seoul, Korea, Republic of; ²Caltech, Pasadena, CA;

³Psychiatry, UCLA Semel Inst. For Neurosci. and Human Behavior, Toronto, ON, Canada;

⁴UCLA, Los Angeles, CA; ⁵Univ. of California, Berkely, Berkely, CA; ⁶Psychological and Brain Sci., Univ. of Iowa, Iowa City, CA

Abstract: Anxiety and depression are highly prevalent mental health disorders that frequently co-occur and share substantial symptom overlap, particularly in altered reward learning. Both conditions are generally associated with deficits in reward processing, marked by reduced responsiveness to gains and increased sensitivity to losses. Discovering computational markers based on reinforcement learning that disentangle anxiety and depression is critical for precise characterization of both their unique and shared pathophysiology. To address this gap, we analyzed clinical survey and behavioral task data from a large-scale sample (N=1,010). Participants completed questionnaires measuring state and trait anxiety (STAI-S, STAI-T), depression (BDI), and performed a modified probabilistic reversal learning task. In the task, two stimuli were presented each trial, drawn from a set of three stimuli. Reward contingencies for each stimulus were reversed three times throughout the session. The task included separate gain and loss conditions that were presented in alternating blocks. To first demonstrate that behavior was driven by outcomes, we performed logistic regression to predict current choices from outcomes of the previous five trials, which revealed significant effects of past rewards, indicating reward-based learning. We then used linear regression to quantify differences in performance between groups. We found that better behavioral performance was associated with lower trait anxiety and higher depression. We fit computational models to the behavior to estimate individual parameters and quantify mechanistic differences in learning between groups. We compared Q-learning models with separate learning rates for different conditions (positive/negative outcomes in gain/loss contexts) that incorporated other components such as forgetting, choice perseverance, and action history bias. The best-performing model with the lowest LOOIC, included four learning rates (positive/negative outcomes in gain/loss contexts), inverse temperature, and choice bias. Depression scores were negatively correlated with learning rates for positive outcomes (no loss) in the loss condition ($\beta=-0.06$, $t=-2.29$, $p=0.02$), after controlling for state and trait anxiety. This result aligns with the anhedonic symptoms of depression, which are characterized by blunted reward sensitivity, and suggests that this blunting

may extend to learning from outcomes such as avoiding losses in the loss context. These findings suggest distinct computational profiles for anxiety and depression, influencing reinforcement learning through different mechanisms.

Disclosures: J. Lee: None. C. Grossman: None. J.D. Feusner: None. R. Tadayon Nejad: None. S. Oh: None. J. Cockburn: None. W. Ahn: None. J.P. O'Doherty: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.12/LL12

Topic: I.03. Decision Making

Support: P50 MH132642

Title: The role of the thalamus in dynamic decision-making

Authors: *C. CALDINELLI¹, J.-J. LI², G. CHAO², M. J. ARCARO⁴, A. G. COLLINS³;

¹Univ. of California, Berkeley, Berkeley, CA; ³UC Berkeley, Psychology Dept., ²UC Berkeley, Berkeley, CA; ⁴Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The thalamus lies in a pivotal position as an integrative hub for areas involved in high-level cognition. Despite its important theoretical role in many computational models and its involvement in psychiatric disorders, the human thalamus has not been studied extensively in the context of higher-level cognition and cognitive flexibility. However, studies with non-human animals show involvement of the mediodorsal nucleus (MD) and the prefrontal cortex (Rikhye et al., 2018) during rule representation and switching, and dysfunction of hub regions is associated with behavioral and cognitive impairment (Bassett et al., 2009; van den Heuvel et al., 2013). Executive function processes require dynamic and flexible coordination of information across brain-wide cortical networks, and the thalamus appears well positioned to perform such integrative processes through its extensive and convergent connections with the prefrontal cortex (Fiebelkorn et al., 2019; Saalman et al., 2012). We developed a novel behavioral task aimed at eliciting frequent switches between rule exploitation and rule exploration (Donoso et al., 2014) and adapted this task for use with fMRI to measure responses in the thalamus and prefrontal cortex. We tested 40 participants (mean age=20.44 years, 29 females and 11 males) while undergoing a task-fMRI scan to probe the involvement of MD during rapid rule switching under uncertainty. Behavioral results show participants integrate reward uncertainty with task structure knowledge to explore rules efficiently, and the computational modeling used was able to retrieve exploration and exploitation periods as well as switches between the two. Task-fMRI results show activation ($z > 3.1$, $p < 0.001$) in prefrontal areas during rule exploration but not exploitation and MD shows activation ($z > 3.1$, $p < 0.001$) during switch trials, supporting our prediction that MD is important to integrate information in dynamically changing and ambiguous environments. Additionally, a region of interest analysis revealed that the portion of the thalamus most strongly

connected to the frontoparietal network during rest showed selective activation during switch trials ($t(39)=2.55$, FDR-corrected $p=0.003$) but not during non-switch trials, further supporting the specific role of thalamic-cortical circuits in cognitive flexibility. These results suggest a primary role of MD in enabling the integration of information in dynamically changing and ambiguous environments such as solving a problem in the presence of uncertainty and updating the rules required to achieve a goal through the extensive and reciprocal connections between the frontal and parietal cortices.

Disclosures: C. Caldinelli: None. J. Li: None. G. Chao: None. M.J. Arcaro: None. A.G. Collins: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.13/LL13

Topic: I.03. Decision Making

Title: Persistent representation of a prior schema in the orbitofrontal cortex facilitates learning of a conflicting schema

Authors: *I. MAOR¹, J. ATWELL¹, I. ASCHER¹, Y. ZHAO², Y. K. TAKAHASHI¹, E. E. HART³, F. PEREIRA², G. SCHOENBAUM¹;

¹NIDA/NIH, Baltimore, MD; ²NIMH/NIH, Bethesda, MD; ³Dept. of Psychology, Univ. of Maryland, College Park, MD

Abstract: Schemas facilitate efficient behavior in novel contexts, but reliance on prior knowledge can hinder flexibility when new demands conflict, an effect implicated in psychiatric disorders. The orbitofrontal cortex (OFC) is known to support schema-based behavior in familiar settings, yet its role during the acquisition of a conflicting schema remains unclear. Here, we addressed this by recording single-unit activity from the OFC of rats learning odor-guided tasks with identical sensory input but orthogonal rules governing reward. Rats were trained on two odor sets (A and B; 8 cues each) under a "non-match" rule, in which reward depended on responding to an odor different from the one sampled on the previous trial. After mastering this schema, the same odors were used in a second phase governed by a "cue-identity" rule, where specific odors predicted reward regardless of prior trials. As expected with schema formation, OFC neurons and ensemble activity rapidly adapted to encode the relevant rule, with faster learning and neural adaptation on subsequent problems. Critically, when rats acquired the second, conflicting schema, OFC neurons maintained persistent traces of the original rule, even after their behavior fully conformed to the new one. This mixed representation was absent in control rats trained solely on the second schema. Moreover, persistent encoding of the prior rule was positively correlated with learning of the new one, suggesting that OFC representation of the prior schema did not interfere with, but rather supported, acquisition of new, conflicting

information. These findings reveal that OFC can independently encode old and new schemas, enabling flexible learning while preserving previously acquired knowledge.

Disclosures: I. Maor: None. J. Atwell: None. I. Ascher: None. Y. Zhao: None. Y.K. Takahashi: None. E.E. Hart: None. F. Pereira: None. G. Schoenbaum: None.

Poster

PSTR047: Reinforcement Learning and Decision-Making

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR047.14/LL14

Topic: I.03. Decision Making

Support: Wellcome 096689/Z/11/Z
Wellcome 220296/Z/20/Z

Title: Neural Representations of Abstract Cognitive Maps in Prefrontal Cortex and Medial Temporal Lobe

Authors: *J. SELVANAYAGAM^{1,2}, J. BUTLER^{2,4}, E. GUTIERREZ^{2,4}, S. VESELIC^{2,4}, T. E. J. BEHRENS^{3,5}, S. W. KENNERLEY^{2,4};

²Dept. of Exptl. Psychology, ³Wellcome Ctr. for Integrative Neuroimaging, ¹Univ. of Oxford, Oxford, United Kingdom; ⁴Dept. of Clin. and Movement Neurosciences, ⁵Sainsbury Wellcome Ctr. for Neural Circuits and Behaviour, Univ. Col. London, London, United Kingdom

Abstract: Grid cells in entorhinal cortex are known to support spatial navigation through hexagonal firing fields that tile physical space. Combined with place cells, these cells support “replay”, a phenomenon wherein sequences of spatial locations are reactivated during rest or sleep, thought to underlie memory consolidation and planning. More recently, analogous grid-like codes have been reported in humans and non-human primates during reasoning over abstract spaces, suggesting that grid codes may constitute a general neural algorithm for organizing knowledge beyond physical dimensions. Recent work from our group has revealed that macaques represented choices as navigation trajectories in a value space supported by a grid-like code in ventromedial prefrontal cortex (PFC). It is of interest to examine how PFC and medial temporal lobe (MTL) neurons represent cognitive map-based computations in abstract, non-spatial tasks.

Here, we trained a rhesus macaque to learn and navigate a 9×12 discrete graph structure comprised of 108 unique images; these individual states are orthogonally connected, mimicking a two-dimensional abstract “maze”. The subject was trained to (1) navigate towards a target state by selecting from the neighbours to the current state, and (2) perform a two-alternative forced-choice task to select which of two candidate target states is closer (geodesic distance) to a given start state. To date, we have recorded 398 single neurons from orbitofrontal cortex, dorsal anterior cingulate cortex, and areas 10/32 as the subject completed Task 1.

Preliminary analyses reveal neurons with fields of increased discharge activity for certain

adjacent states. Strikingly, 6-9% of neurons across regions exhibited statistically significant grid-like periodicity in their firing patterns over the abstract 2D graph for the current state at the moment of choosing the next state. These findings provide early evidence that grid-like codes support flexible reasoning in abstract cognitive maps.

Behavioural analyses from Task 2 reveal the subject accurately judges distances up to 8 states away, highlighting the ability to probe long distance relationships within the graph. We will acquire ultra-high-density recordings, simultaneously from PFC and MTL, to examine grid codes, and neural replay, as the subject makes decisions in a discrete, abstract space.

In sum, these results build on growing evidence that spatial coding principles are repurposed for non-spatial knowledge structures. Together with our upcoming simultaneous PFC-MTL recordings, these data will provide key insights into how cognitive map-based computations support higher-order cognition.

Disclosures: J. Selvanayagam: None. J. Butler: None. E. Gutierrez: None. S. Veselic: None. T.E.J. Behrens: None. S.W. Kennerley: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.01/LL15

Topic: I.11. Language

Support: Fondecyt Regular 12411884
Grant 2024AFB240004 from the Agencia Nacional de Investigacion y Desarrollo (ANID).

Title: Brain Responses to Early Speech Perception in Preterm and Full-Term Infants

Authors: *A. HELO^{1,2}, G. MORENO², M. FERNANDEZ GALLARDO², V. VARELA²;

²Dept. of Speech, Language, and Hearing Sci., ¹Univ. of Chile, Santiago, Chile

Abstract: Infants born preterm are at elevated risk for language delays. Early perceptual skills, such as sensitivity to speech sound contrasts, are foundational for language development. Although previous studies have reported differences in linguistic perceptual processing between preterm and full-term infants, the evidence remains inconclusive. Moreover, no prior study has directly compared ERP responses to both native phonemic (vowel and consonant) and stress contrasts in this population. We recorded EEG from 11 preterm infants (born 30-33 weeks of gestation; 55% girls) and 18 full-term controls (born 37-40 weeks of gestation; 39% girls), all from Spanish-monolingual families. Infants listened to a passive auditory oddball paradigm, in which the standard stimulus was /du'du/ (a bisyllabic pseudoword with penultimate stress). Three deviant conditions were presented: consonant change (/tu'du/), vowel change (/do'du/), and stress change (/du'DU/). EEG was recorded from left frontal electrodes (F3, FC3), and mismatch response (MMR) amplitudes were analyzed in the 300-500 ms post-stimulus window.

Additionally, we measured the amount of caregiver speech input, using adult word count derived from LENA recordings. Linear models tested the effect of group (preterm vs. full-term) and amount of caregiver speech input on MMR amplitude for each condition. A marginal group effect was found for the consonant contrast ($\beta = -2.36$, $p = 0.059$), suggesting reduced discrimination in preterm infants. No significant effects were found for vowel or stress contrasts, and caregiver speech input did not significantly predict neural responses. These preliminary findings suggest that neural discrimination of consonantal information may be particularly vulnerable in preterm infants by six months of age. Reduced MMRs to speech contrasts may reflect early differences in auditory processing that precede later language outcomes. Ongoing work will examine developmental trajectories and associations with emerging vocabulary.

Disclosures: A. Helo: None. G. Moreno: None. M. Fernandez Gallardo: None. V. Varela: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.02/LL16

Topic: I.11. Language

Support: E. H. Solomon Center for Neurodevelopmental Research

Title: Auditory Training in Infants Impacts Task-Evoked and Spontaneous Activity Across Development

Authors: *B. MAHMOOD¹, T. REALPE-BONILLA¹, L. MILOVIC¹, A. A. BENASICH²;
¹Rutgers Univ., Newark, NJ; ²Rutgers University-Newark, Newark, NJ

Abstract: Both spontaneous and task-evoked cortical activity aid in the formation of stable and efficient networks during development via activity-dependent mechanisms. Studies show that spontaneous and task-evoked activity coevolve in early development, indicating that these two types of activities are not separate but interact with one another. Given that early development is a time of incredible plasticity, changes in either form of activity can induce dramatic changes in the other, and consequently, influence overall network formation. In the current study, dense-array EEG was collected at 6, 9 and 18 months to examine whether task-evoked activity is improved in infants following a six-week auditory training experience provided between 6.5-8 months-of-age. Additionally, frontal spectral power was calculated from spontaneous EEG (sEEG) activity at all three ages. Results show that infants that had been trained have faster recognition, as well as quicker discrimination of rapidly presented auditory cues, skills that are crucial for language development. Moreover, these same infants displayed a greater rate of increase in high frequency frontal spontaneous power, i.e. gamma power. Furthermore, higher spontaneous frontal gamma power was correlated with higher scores on standardized behavioral assessments. These results show how early auditory environment is particularly important for the

refinement of acoustic maps, affecting both task and spontaneous activity, which in turn may cascade into better cognitive abilities like language.

Disclosures: B. Mahmood: None. T. Realpe-Bonilla: None. L. Milovic: None. A.A. Benasich: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.03/LL17

Topic: I.11. Language

Support: E. H. Solomon Center for Neurodevelopmental Research

Title: Impacts of an interactive auditory experience on infants at familial risk of neurodevelopmental disorders

Authors: *L. A. MILOVIC¹, N. A. CHOUDHURY², T. REALPE-BONILLA³, C. P. ROESLER³, A. A. BENASICH³;

¹Rutgers University, Ctr. for Mol. and Behavioral Neurosci., Newark, NJ; ²Ramapo Col. of New Jersey, Mahwah, NJ; ³Rutgers Univ., Newark, NJ

Abstract: Efficient temporal processing is critical for the foundation of language. Studies have shown that the ability to detect and characterize brief and successive auditory stimuli is a challenge for individuals with neurodevelopmental disorders, and that infants born into families with such disorders are at increased risk for developing temporal processing deficits. Early interventions, such as the interactive auditory experience (IAE), target the neural underpinnings that contribute to these skills well before language is acquired. The IAE utilizes an operant paradigm to fine-tune acoustic processing strategies at a critical period of development from 4 to 7 months of age. In this study, prelinguistic neural processing after IAE was examined for infants with a family history of neurodevelopmental disorders (*FH+*) in contrast to infants without a family history (*FH-*, *n*=26) and naive controls (*n*=22). The *FH+* group includes infants with a familial history of language learning impairment (*LLI*, *n*=11) (e.g. dyslexia, auditory processing disorder, etc.), attention-deficit hyperactivity disorder (*ADHD*, *n*=10), or autism spectrum disorder (*ASD*, *n*=6). Electroencephalography (EEG) was recorded during a passive auditory oddball task (70ms interstimulus interval complex tone stimuli) and nonparametric permutation analysis of event-related potentials (ERPs) was used to assess how infants differentially responded to the acoustic stimuli. Previous research has demonstrated that infants who participated in the IAE showed enhanced neural discrimination (N2*/P2). Here, we show that the morphology of the standard tone waveform for the *LLI FH+* subgroup mirrors that of the naive controls; however, when presented with an oddball tone, a difference in the N2*/P2 discrimination component (at ~470ms) was identified. IAE enhanced processing of *LLI FH+* infants to be similar to typical maturation seen at 7 months of age. The sensory and

discriminatory responses of *ADHD FH+* infants resembled *FH-* infants who had received the IAE. A late positivity (at ~660ms) in the left frontocentral area may reflect attentional differences of *ADHD FH+* infants following the presentation of an oddball tone. *ASD FH+* infants showed a positivity ~50ms following the presentation of a standard tone, perhaps indicative of sensory gating in the frontocentral area and thus a unique response to the ERP paradigm and IAE. The time windows discussed emphasize the fundamental differences across *FH+* infants with varying risk profiles. These exploratory findings are important to further the understanding of how *FH+* infants differ mechanistically at a young age and the cortical plasticity targeted by the IAE.

Disclosures: L.A. Milovic: None. N.A. Choudhury: None. T. Realpe-Bonilla: None. C.P. Roesler: None. A.A. Benasich: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.04/LL18

Topic: I.11. Language

Support: FONDECYT 1241884

Title: Amount of Speech Directed to Infants Predicts Basal Oxytocin Levels in Six-Month-Old Infants: Preliminary Evidence from Preterm and Full-Term Groups

Authors: *G. MORENO¹, V. PÉREZ¹, A. HELO², A. MUNOZ¹, P. MALDONADO³;
¹Univ. de Chile, Santiago, Chile; ²Univ. of Chile, Santiago, Chile; ³Synapse and Network Develop., Netherlands Inst. For Neurosci., Amsterdam, Netherlands

Abstract: Oxytocin, a neuropeptide involved in social bonding and neural plasticity, has been proposed as a key mediator of the effects of early social experiences on brain development. While experimental studies link oxytocin release to social interaction, little is known about how naturalistic caregiver-infant experiences, such as linguistic input, relate to basal endogenous oxytocin levels in infancy.

This preliminary study examined whether caregiver speech input predicts basal salivary oxytocin levels in six-month-old infants, and whether this association varies by birth status or feeding type. We analyzed data from 11 preterm infants (born 30-33 weeks of gestation; 55% girls) and 18 full-term infants (born 37-40 weeks of gestation; 39% girls), all from Spanish-monolingual families. Saliva samples were collected approximately one hour after feeding (breast or bottle), before any structured interaction. The quantity of caregiver speech input was measured over one typical day using the Language Environment Analysis (LENA) system, with adult word count (AWC) as the main variable. A linear regression model assessed the effects of AWC, group (preterm vs. full-term), and feeding type on oxytocin levels.

Results showed a significant positive association between caregiver speech input and infant

oxytocin levels ($\beta = 0.013$, $p = 0.007$), indicating that greater linguistic input is related to higher basal oxytocin concentrations. No significant effect of group ($p = 0.053$) or feeding type ($p = 0.63$) was found. The model explained 60% of the variance in oxytocin levels ($p = 0.033$), suggesting that the observed association between speech exposure and oxytocin is robust and independent of delivery status or feeding method.

These findings offer preliminary support for the hypothesis that everyday linguistic environments are biologically meaningful in infancy. Ongoing research will assess whether oxytocin mediates the effect of early language input on brain maturation and developmental outcomes in at-risk populations.

Disclosures: G. Moreno: None. V. Pérez: None. A. Helo: None. A. munoz: None. P. Maldonado: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.05/LL19

Topic: I.11. Language

Support: NIH DP5 OD031843

Title: Cross-frequency dynamics and localization during contextualized language comprehension

Authors: *A. JANSON¹, C. HONG², T. S. FOTIDZIS³, K. ABOUD¹;

¹Special Educ., Vanderbilt Univ., Nashville, TN; ²Vanderbilt Univ., NASHVILLE, TN;

³Vanderbilt Univ., Nashville, TN

Abstract: Language comprehension (LC) is a complex cognitive process that engages multiple brain networks across multiple timescales and frequencies. Coordination across networks requires dynamic shifts in neural frequency that allow for layered, hierarchical communication. Limitations in spatial and temporal resolutions across brain imaging modalities have historically prevented real-time characterization of the frequency dynamics of widespread LC networks. Our objective was to implement a novel fused MRI-EEG and Continuous Wavelet Transform (CWT) analysis to identify frequency “fingerprints” for key language networks during naturalistic language comprehension. Fused functional MRI (fMRI) and EEG were used to investigate 45 adults (age 25.7 yrs, 16 male) who were right-handed, native English speakers with typical reading ability. Stimuli were presented as two blocks of jumbled words (word baseline) and two blocks of expository text (passages). Joint independent component analysis (jICA) was used with paragraph-level inputs (8 per subject) and computed across subjects (Infomax with 50 iteration ICASSO). 30 total components were generated, and post-hoc component groups were split between word baseline and passages. CWT analysis was bootstrapped with 10,000 gaussian noise simulations to determine significant frequency power. Two sample t-tests were performed

on the jICA group weights. Finally, CWT was performed on the EEG components to analyze frequency power changes over the 1 s post-stimuli window. Confirmatory analysis found that passage reading was associated with increased theta and gamma power compared to the word baseline. Joint ICA analysis revealed three joint components that showed significantly greater engagement during passages ($p < 0.001$, Bonferroni-corrected), with spatial expression across canonical language regions, the left-lateralized default mode network (DMN), and bilateral dorsal angular gyrus. Frequency analyses revealed that the language component exhibited prolonged theta with nested beta bursts; the DMN component was dominated by prolonged alpha with synchronized beta-gamma bursts; and the angular gyrus component showed shifting activity from beta and alpha to beta and theta. Using fused fMRI-EEG, we identified distinct frequency-network signatures supporting passage comprehension. Our findings highlight multiscale dynamics across language and extended language networks, including nested beta-gamma activity in the DMN and rhythmic switching in angular gyrus, suggesting that naturalistic reading comprehension relies on temporally coordinated engagement across spatially distributed brain systems.

Disclosures: A. Janson: None. C. Hong: None. T.S. Fotidzis: None. K. Aboud: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.06/LL20

Topic: I.11. Language

Title: Individual differences in emotion and language functions revealed in dynamic brain responses to movie clips

Authors: *X. WEI^{1,2,5}, M. J. MARTE^{1,6}, L. RIGOLO³, C. P. GALVIN⁴, Y. TIE^{3,5}, E. LIEBENTHAL^{1,5};

¹McLean Hosp., Belmont, MA; ³Neurosurg., ⁴Dept. of Neurosurg., ²Brigham and Women's Hosp., Boston, MA; ⁵Harvard Med. Sch., Boston, MA; ⁶Boston Univ., Boston, MA

Abstract: ‡Einat Liebenthal and Yanmei Tie contributed equally as senior authors.

Movie clips with different content may elicit distinct brain responses and hold different power for predicting individual behaviors. We investigated how individual emotional and language functions are reflected in the brain's dynamic responses during movie viewing. We used functional magnetic resonance imaging (fMRI) data acquired at 7 Tesla during movie-viewing (3 clips from Hollywood movies, 918 s total duration), in 176 healthy subjects participating in the Human Connectome Project (HCP). For each subject, five measures of emotional function were assessed: Emotion Recognition (ER), Negative Affect, Psychological Well-being (PW), Social Relationships (SR), and Stress and Self-Efficacy (SSR). In addition, two language measures—Reading Decoding (RD) and Vocabulary Comprehension (VC)—were included. The fMRI data were analyzed across 229 cortical regions defined in the HCP MMP 1.0 atlas and 4 subcortical

regions defined in the Harvard-Oxford atlas. These 233 regions were identified as relevant to emotion and language processing based on a meta-analysis conducted in Neurosynth. We employed a sliding window (window size= 30 s; step size= 1 s) dynamic intersubject correlation (dISC) analysis to compute the momentary synchrony of each individual with the mean of all other individuals in the group. We then used a General Linear Model (GLM) to estimate the correlation between each behavioral measure and the dISC value within each time window for each individual. We found that (1) during viewing of specific movie scenes, individual differences in emotional and linguistic function significantly influence the brain synchronization with all other individuals in the group. (2) Higher scores (better function) on ER, RD and VC were associated with higher dynamic ISC scores at multiple time points, whereas higher scores (lower function) on NA, SR, SSE and PW (better function) were associated with lower dynamic ISC ($p < 0.05$, cluster-wide correction). (3) Brain activity during movie viewing shows behavior-specific patterns. For example, the top regions showing significant correlations (in more than 5% of time windows) for NA were in the left temporoparietal junction, bilateral parietal lobe, cingulum, and right prefrontal cortex; and for reading in the bilateral superior temporal gyri, left middle temporal cortex, and inferior frontal sulcus. These findings suggest that individuals with more similar emotional and linguistic functions display more synchronized activation in emotional and language brain regions during viewing of certain movies scenes.

Disclosures: X. Wei: None. M.J. Marte: None. L. Rigolo: None. C.P. Galvin: None. Y. Tie: None. E. Liebenthal: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.07/LL21

Topic: I.11. Language

Support: University of Macau Development Foundation Grant EXT-UMDF-014-2021
University of Macau Grant MYRG-CRG2024-00047-ICI, MYRG2022-00265-ICI, MYRG2022-00200-FAH, CPG2023-00016-FAH, CRG2021-00001-ICI
NIH Grant R01 MH081990

Title: Phase-encoded fMRI revealed rapid switching between overt language production and micro resting state

Authors: *R.-S. HUANG¹, M. WANG^{1,2}, T. LEONG¹, U.-M. LEI¹, V. LEI¹, D. LI¹;
¹Univ. of Macau, Macau, China; ²Shenzhen Polytechnic Univ., Shenzhen, China

Abstract: The default mode network (DMN) is known to deactivate during external goal-oriented tasks, including overt speech production. However, understanding the interaction

between language processing and the DMN, and how swiftly one can switch from complex naturalistic language tasks to a resting state, requires resolving the relative timing between task engagement and DMN activity. Here, we used phase-encoded fMRI to explore brain dynamics in tasks with alternating periods of overt speech production and rest. We used phasor diagrams to characterize the timing and strength of activations in language networks and the DMN, aiming to identify the role of DMN in language processing. Thirty-one native Mandarin (L1) speakers (23.3 ± 4 years) with English as their second language (L2) were scanned in one L1 and one L2 fMRI sessions. Each session included two 256-s scans for each of the following tasks involving sentence-level processing: (1) 5-s silent reading, (2) 5-s reading aloud, (3) 5-s silent reading then 5-s reciting, (4) 5-s listening, (5) 5-s shadowing, and (6) 5-s listening then 5-s reciting. Each scan comprised 16 trials of 16-s task-rest alternation (rest period: 11 s for tasks 1, 2, 4, and 5; 6 s for tasks 3 and 6). Time series of fMRI data were analyzed using Fourier-based methods, displaying the amplitudes and phases of signals at 16 cycles/scan on the cortical surface. Surface-based regions of interest (sROIs) were outlined for language (task-positive) networks and core regions of DMN, including dorsal and ventral medial prefrontal cortex (dmPFC and vmPFC), posterior cingulate cortex, and angular gyrus. A phasor was computed by vector-averaging all complex F-statistics values within each sROI. Language comprehension tasks 1 and 4 (with an 11-s rest per trial) did not induce significant changes in DMN. All other tasks involving overt production significantly activated all DMN regions, with the strongest activation observed in vmPFC. The vmPFC phasors show an approximate 5-s delay compared to task-positive phasors in tasks 2 and 5. However, they are approximately antiphase to each other in tasks 3 and 6. The phases of the other DMN regions fall between those of the vmPFC and task-positive regions. Activation amplitudes in all DMN regions in the left hemisphere increased with task demands, from comprehension only, to immediate production, and to delayed production involving working memory. In summary, phase-encoded fMRI revealed rapid switching of activations between language networks and DMN on the scale of several seconds. The activation amplitudes and phases in DMN depend on the demands of language tasks, with different levels of engagement among the core DMN regions.

Disclosures: R. Huang: None. M. Wang: None. T. Leong: None. U. Lei: None. V. Lei: None. D. Li: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.08/LL22

Topic: I.11. Language

Support: SNSF Grant P500PS_225257

Title: Information dynamics underlying speech perception

Authors: *C. ODERBOLZ¹, J. ORPELLA²;

¹Dept. of Neurosci., Georgetown Univ. Med. Ctr., Washington, DC; ²Dept. of Neuroscience, Georgetown Univ. Med. Ctr., Washington, DC.

Abstract: The analysis of the speech signal unfolds within a distributed network of brain regions that extract critical acoustic and linguistic features. An important question concerns how the brain orchestrates the processing of the various kinds of information for successful speech perception, i.e. what the underlying information dynamics in the speech and language network are. We use information theoretical measures to characterize these dynamics (Francis et al. 2022). First, we validate our methods by applying them to fMRI data from a binaural integration task (Preisig et al. 2021). In this task, an ambiguous speech sound (a CV syllable midway between /da/ and /ga/) is presented to the right ear while a disambiguating spectral feature (third formant) is presented to the left ear. Because the successful completion of this task (i.e. the integration of unique acoustic features) is fully reflected in a listener's behavior (i.e. the identification of a CV syllable), it allows us to understand how the dynamics of information processing inform perception. Next, we probe the information dynamics underlying the classification of a critical linguistic feature, i.e. sentence type. Acoustically, the distinction between a question and a statement is cued by a rising or a falling fundamental frequency (f0) contour (Studdert-Kennedy and Hadding 1973). We analyze source-localized MEG data from a recent experiment in which participants listened to and classified single words according to sentence type (Oderbolz et al., submitted). The words' f0 contours were manipulated to create a continuum between a prototypical question and statement. In a forthcoming paper, we show that the behaviorally-relevant representation of the sentence type distinction lies in the left frontocentral operculum and anterior insula (Op/aINS). We now reveal that the left Op/aINS receives a high degree of unique information from the right hemisphere, especially regions in the frontal and temporal cortex, in line with its specialization for slowly changing acoustic signals (Oderbolz, Poeppel, and Meyer 2025). In turn, the left early auditory and inferior frontal cortex contribute redundant as well as synergistic information. Together, these information dynamics interact to produce the neural representation of sentence type that informs behavior. Conceptualizing information as a dynamic and decomposable entity by means of information theory provides the necessary nuance to understand how complex cognition and behavior arise. Although we apply these measures to questions relevant to speech and language, we emphasize their potential in both basic and clinical research and in a wide range of fields.

Disclosures: C. Oderbolz: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.09/MM1

Topic: I.11. Language

Support: NIH Grant R01-DC020960 to S.N.H.

Title: Representational disentangling of spoken words and talker identity in the human auditory cortex

Authors: *A. BANDREDDI¹, D. BOEBINGER¹, D. SKRILL³, K. V. NOURSKI⁴, M. A. HOWARD, III⁵, C. M. GARCIA⁶, T. WYCHOWSKI⁷, W. H. PILCHER⁸, S. V. NORMAN-HAIGNERE²;

²Biostatistics & Neurosci., ¹Univ. of Rochester, Rochester, NY; ³Univ. of Rochester Med. Ctr., Rochester, NY; ⁴The Univ. of Iowa, Iowa City, IA; ⁵Dept. of Neurosurgery, Univ. of Iowa Hosp. and Clinics, Iowa City, IA; ⁶Neurosurg., Univ. of Iowa, Iowa City, IA; ⁷Neurol., Univ. of Rochester, Sch. of Med. and Dent., Rochester, NY; ⁸Div. Neuroendocrinol, Univ. Rochester Sch. Med., Rochester, NY

Abstract: Complex natural sounds such as speech contain many different sources of information, but recognizing these distinct information sources is computationally challenging because they are highly entangled in the acoustic waveform that reaches the ear. For example, variation in the acoustic attributes of different talkers makes it challenging to recognize the identity of a word, while variation in the acoustics of different words makes it challenging to recognize talker identity. How does the auditory system disentangle word identity from talker identity in auditory cortex? While disentanglement has been extensively studied in the visual cortex, less is known about how it is accomplished in the human auditory cortex. One hypothesis is that specific brain regions specialize for coding either word identity or talker identity. Alternatively, word identity and talker identity may be represented by distinct dimensions of the neural code at the population level instead of specific regions. Distinguishing between these two hypotheses has been challenging in part due to the coarse resolution of non-invasive neuroimaging methods such as fMRI. To address this question, we measured neural responses to a diverse set of 338 words spoken by 32 different talkers using spatiotemporally precise intracranial recordings from the auditory cortices of neurosurgical patients undergoing chronic invasive monitoring for medically intractable epilepsy. We developed a simple set of model-free experimental metrics for quantifying representational disentangling of word and talker identity, both within individual electrodes and brain regions, as well as across different dimensions of the neural population response. We observed individual electrodes in speech-selective regions of non-primary auditory cortex that show a representation of words that is partially robust to acoustic variation in talker identity, but no electrodes or brain regions showed a robust representation of talker identity. However, at the population level, we observed distinct dimensions of the neural response that nearly exclusively coded either words or talker identity. These results suggest that while there is partial specialization for talker-robust word identity in localized brain regions. Robust disentangling is accomplished at the population level with distinct representations of words and talker identity mapped to distinct dimensions of the neural code for speech.

Disclosures: A. Bandreddi: None. D. Boebinger: None. D. Skrill: None. K.V. Nourski: None. M.A. Howard: None. C.M. Garcia: None. T. Wychowski: None. W.H. Pilcher: None. S.V. Norman-Haignere: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.10/MM2

Topic: I.11. Language

Support: NIH Grant U01AG052564

Title: Relationships between brain structure and language experience in older adults

Authors: *A. J. KRAFNICK¹, A. M. LEAVER²;

¹Dominican Univ., River Forest, IL; ²Radiology, Northwestern Univ., Chicago, IL

Abstract: Whether learning multiple languages changes the brain and domain general cognitive skills remains an important and interesting question for neuroscience. Potential benefits have been reviewed and debated at length (e.g. Bialystok, 2017; Antoniou, 2019), and models of brain changes (Grundy et al., 2017; Pliatsikas, 2020) provide valuable frameworks for discussing these differences in language experience. However, several factors can influence the findings of individual studies looking at language experience and the brain, such as age, age of acquisition, proficiency, education, number of languages known, and many others. These factors, along with differences in reporting cohort demographics has led to less clarity across studies (Garcia-Penton et al., 2016; Danylkiv & Krafnick, 2020), highlighting the need for continued investigation. Here, we used data from the HCP-Aging dataset (Bookheimer et al., 2018) to investigate whether brain structure differs between monolinguals and multilinguals, and whether structure in those areas correlates with age of acquisition of the second language. Subjects from the HCP-Aging dataset were classified as monolingual or multilingual (any reported multilingual experience) using the Language Experience and Proficiency Questionnaire (LEAP-Q; Marian et al., 2007). As expected, one language was the most reported (N=513) with 150 subjects, 38 subjects, and 17 subjects reporting two, three, and four languages respectively, for a total sample size of 718 (513 monolingual, 205 multilingual). To look at differences between these groups, FreeSurfer output metrics (volume, cortical thickness, and cortical surface area) were compared while controlling for age, sex, education, and data collection site. For those areas, correlation between the FreeSurfer metric with reported acquisition age of the second language was interrogated, again controlling for age, sex, education, and data collection site. Multilinguals showed less cerebellum cortical volume in both left and right hemispheres, and less white matter volume in left superior frontal and right pars orbitalis frontal areas (FDR corrected $p < 0.05$ within metric). Additionally, left and right hemisphere angular gyrus showed greater cortical thickness in multilinguals compared to monolinguals ($p < 0.05$, uncorrected). Within multilinguals, left superior frontal and right pars orbitalis showed less white matter volume in early compared to late second language learners. These preliminary findings continue to provide support for brain changes related to language experience, and the need to fully understand mitigating factors.

Disclosures: A.J. Krafnick: None. A.M. Leaver: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.11/MM3

Topic: I.11. Language

Support: NIH R01DC04290
NIH U01NS137991
NSF SBE2342847
MRC U.K. MR-T032553-1
NIH S10RR028821

Title: Laminar information flow for working memory and language: Insights from human laminar fMRI and intracortical neuronal recordings

Authors: Y. A. AYALA¹, H. CAFFARATTI², R. M. CALMUS¹, J. I. BERGER¹, D. CHRISTIANSON², A. E. RHONE¹, F. DE MARTINO⁴, E. S. YACOUB⁵, V. A. MAGNOTTA², L. MELLONI⁶, T. A. VALIANTE⁷, K. ULUDAG⁸, T. D. GRIFFITHS⁹, M. ZANATY², H. KAWASAKI¹, S. CHATTERJEE³, T. ABEL³, M. A. HOWARD, III¹, J. D. W. GREENLEE¹, *C. I. PETKOV²;

¹Neurosurg., ³Neurosci. and Pharmacol., ²Univ. of Iowa, Iowa City, IA; ⁴Fac. of Psychology, Maastricht Univ., Maastricht, Netherlands; ⁵Univ. of Minnesota, Minneapolis, MN; ⁶Neurosci., Max Planck Inst. for Empirical Aesthetics, Frankfurt Am Main, Germany; ⁷Univ. Hlth. Network, Toronto, ON, Canada; ⁸Univ. of Toronto, Toronto, ON, Canada; ⁹Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: The extent to which human language functions interact with those for domain-general cognition across the cortical layers is unknown. Studies of dorso-lateral prefrontal cortex (DLPFC) in nonhuman primates have implicated layer 3 neurons in a recurrent circuit for working memory (WM), and a canonical microcircuits model describes laminar interactions between brain areas. Here, we focus on DLPFC, often implicated in WM but more equivocally in language function, to test the hypothesis of a neural entanglement between WM and language combinatorial functions across layers. In our task, participants heard two or three words, and they either alphabetized or maintained the word order during the delay, after which they verbally reported their mental word order. On a trial-by-trial basis, participants manipulated the words into or out of a grammatical order. We analyzed high-density laminar array recordings obtained from DLPFC during deep-brain stimulation procedures in two neurosurgery patients and one from superior temporal gyrus in a tumor patient. These extracellular recordings were compared with cortical depth-dependent laminar fMRI (0.8 mm isotropic voxel size), capable of resolving sets of layers and broader system interactions, in the three patients scanned preoperatively. Laminar array recordings from DLPFC showed that single neurons across the cortical layers were modulated by all task components. Most neurons' firing rates decreased as the patient listened to each word and increased both at the beginning of the WM delay period and during the vocal production period. Neurons with WM-specific effects were distributed in both superficial and deep layers. The language grammatical effects, although expectedly weaker in DLPFC than those for WM, engaged both superficial and deeper layers. The laminar fMRI results

recapitulated several of the laminar array recording findings, and they showed overlapping clusters for grammatical and WM effects in a network of regions, including DLPFC. In a separate cohort of epilepsy and tumor patients, samples from tissue that required clinical resection were obtained prior to and after task performance by the patients during their operating room procedure. The samples were analyzed for single-nuclear multi-omics (RNA+ATAC sequencing). The results provide initial insights from cellular to systems levels into the interplay of working memory and language across cortical layers, including from an area in the human brain often identified for its cognitive domain-general function but not necessarily language. * YA, HC & RC joint first; JG & CP joint senior authors.

Disclosures: Y.A. Ayala: None. H. Caffaratti: None. R.M. Calmus: None. J.I. Berger: None. D. Christianson: None. A.E. Rhone: None. F. De Martino: None. E.S. Yacoub: None. V.A. Magnotta: None. L. Melloni: None. T.A. Valiante: None. K. Uludag: None. T.D. Griffiths: None. M. Zanaty: None. H. Kawasaki: None. S. Chatterjee: None. T. Abel: None. M.A. Howard: None. J.D.W. Greenlee: None. C.I. Petkov: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.12/MM4

Topic: I.11. Language

Support: NIH IRP
NIDCD IRP

Title: More Than Strength: Task-Specific Brain Dynamics from Rolling Correlation Analysis

Authors: A. SOBITAN¹, D. THAPLOO², K. WINGERT³, A. KUROSU⁴, *N. BIASSOU⁵;
¹NIDCD / NIH, Bethesda, MD; ²NIDCD, NIDCD, NIH, Bethesda, MD; ³NIDCD, Bethesda, MD; ⁴NIDCD, NIH, Bethesda, MD; ⁵NIH, Oakton, VA

Abstract: Abstract:

Background Cognitive functions often recruit overlapping brain networks, reflecting the principle of neural efficiency in the context of resting state functional magnetic resonance imaging. However, task specific networks reorganize dynamically in response to specific task demands and remain poorly understood. **Methods** In this retrospective study, we applied a jackknife-based dynamic functional connectivity (dFC) approach using Pearson correlation to characterize time-varying network engagement during language (story comprehension) and numerical (math problem-solving) tasks in 172 participants (sex and age matched) from the Human Connectome Project- Young adult cohort. Data were preprocessed using AFNI and FreeSurfer. Cortical regions were defined using the Desikan-Killiany atlas. We used a participation threshold of 85% for consistent network generation. **Results:** Story comprehension showed stronger connectivity in left frontoparietal regions, while math tasks engaged parietal

and interhemispheric networks. Of 87 consistent connections across subjects, 84 (~97%) differed significantly in strength between tasks ($p < 0.001$). Three connections left cuneus-lingual, right superior parietal-right supramarginal, and left superior parietal-right supramarginal, showed equivalent strength, likely reflecting domain-general functions. However, rolling correlation revealed distinct left cuneus-left lingual fluctuations across tasks suggesting differential temporal engagement of this connection depending on cognitive demands. Temporal variability was greater in right and interhemispheric connections, suggesting enhanced flexibility in regions supporting attentional switching and executive control. **Conclusion** These findings underscore the value of integrating connectivity strength and dynamic variability to capture the brain's flexible functional architecture. Our results suggest that task-dependent plasticity is reflected in both the strength and temporal dynamics of core cognitive networks, alongside domain-specific recruitment. The application of jackknife resampling in dFC estimation was critical in uncovering these subtle yet meaningful patterns of network adaptability and cross-domain efficiency.

Disclosures: A. Sobitan: None. D. Thaploo: None. K. Wingert: None. A. Kurosu: None. N. Biassou: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.13/MM5

Topic: I.11. Language

Support: University of Macau Development Foundation Grant EXT-UMDF-014-2021
University of Macau Grant MYRG-CRG2024-00047-ICI, MYRG2022-00265-ICI, MYRG2022-00200-FAH, CPG2023-00016-FAH, CRG2021-00001-ICI
NIH Grant R01 MH081990

Title: Phase-encoded fMRI revealed common and distinct traveling wave formations during overt speech production and wind instrument playing

Authors: *U. LEI, V. LEI, Y. TIAN, M. MU, K. WEATHERLY, D. LI, R.-S. HUANG;
Univ. of Macau, Macau, China

Abstract: To explore language-music links in the brain, prior studies emphasized activation overlaps between domains, with little attention to spatiotemporal brain dynamics. This study used rapid phase-encoded fMRI to map information flow in space and time, comparing traveling wave formations during overt production of sentences and wind instrument (recorder) playing of musical notation, both featuring different metrical structures. Thirty right-handed Cantonese-speaking wind players (22.1 ± 5.92 years) with average English proficiency (Language History

Questionnaire: 0.62 ± 0.03) participated in this study. Each fMRI session consisted of 12 scans, with three conditions per domain, each repeated twice: (1) baseline (no accent marks), (2) congruent (accents aligned with natural phrasing), and (3) incongruent (accents misaligned). In each 16-s period of a 256-s scan, the subject read an English sentence or musical notation, overtly producing it for 6 s, then rested for 10 s. Functional data were analyzed with Fourier methods, displaying amplitudes and phases of periodic activations on the cortical surface. Phase-encoded activation maps revealed significant cortical overlap between language and music tasks. The overlapping regions showing earlier activation phases include auditory, insular, premotor, SMA, and MI/SI (orofacial, respiratory) cortices, which are involved in auditory-motor integration for planning and coordination of production in both domains. Regions showing later activation phases include posterior parietal cortex and manual control regions (wind playing only). Additionally, superior temporal sulcus (STS) and Sylvian-parietal-temporal area (Spt) show greater engagement under congruent and incongruent conditions. These regions support the continuous processing of incoming language or musical sequences with motor execution demands. Notably, rhythmically guided (congruent and incongruent) conditions led to larger overlaps between domains than the baseline condition, with music tasks eliciting extended activation in language-related regions (frontal cortex, STS, and insula). Moreover, a consistent progressive order, from the baseline to congruent to incongruent conditions, was observed in behavioral responses and mean activation phases, highlighting the similar modulatory role of rhythm predictability in both domains. Together, this study revealed common and distinct spatiotemporal dynamic patterns during language and music production, with overlapping traveling waves and similar modulation by rhythm, domain-specific activations, and greater engagement of language areas in rhythm-guided music tasks.

Disclosures: U. Lei: None. V. Lei: None. Y. Tian: None. M. Mu: None. K. Weatherly: None. D. Li: None. R. Huang: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.14/MM6

Topic: I.11. Language

Title: Neural encoding of present but not future story content scales with individual differences in attentional engagement

Authors: *S. GAO¹, Y. LEONG², M. D. ROSENBERG²;
²Dept. of Psychology, ¹Univ. of Chicago, Chicago, IL

Abstract: Neural encoding models have shown that our brain dynamically represents both present and future semantic content when comprehending narratives (Caucheteux et al., 2023). However, an open question is how individual differences in narrative processing affect these representations. In this study, we explored one aspect of this question: whether attentional

engagement benefits the encoding of present semantic information and forecasting of upcoming information in a story. We utilized a publicly available fMRI dataset Le Petit Prince (EN n = 49, Li et al., 2022), where participants listened to an audio story divided into nine 10-min sections. We inferred each participant's level of attentional engagement from neural activity by applying a connectome-based predictive model (CPM) of sustained attention from Rosenberg et al. (2016). To measure neural encoding model performance, we first vectorized semantic information by feeding the transcript of each story section to GPT-2 and extracting time-resolved internal representations. This resulted in a vector corresponding to each story time point, or TR (2 sec). Next, for each ROI in a 122-node whole-brain atlas (Yeo et al., 2011; Fan et al., 2016), we built individually-optimized semantic encoding models (train: sections 1~6; test: sections 7~9) by predicting neural dynamics from vectorized semantic information at each TR. Model performance was evaluated by correlating between predicted and observed ROI time series. Baseline encoding models included contextualized embeddings of tokens within the current TR, and forecasting encoding models additionally included contextualized embeddings of tokens at various lengths (-10 to 40 tokens) from the current TR. Forecasting models predicting ROI activity from present and future semantic content were more accurate in individuals predicted by the CPM to be more attentive. However, individual attentiveness was not related to the success of forecasting models when controlling for present content. Results were consistent across brain networks including the default mode network, implicated in memory integration and narrative engagement. These results suggest that more attentive individuals more strongly encode present semantic information, but not necessarily more strongly forecast upcoming information.

Disclosures: S. Gao: None. Y. Leong: None. M.D. Rosenberg: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.15/MM7

Topic: I.11. Language

Title: Resting-state functional connectivity of bilateral crus i/ii with semantic cortical regions and its association with verbal fluency performance

Authors: *J. DELERIN-CORTES¹, A. REYES AGUILAR², E. A. MORALES³;

¹Dept. of Psychobiology and Neuroscience, Fac. of Psychology UNAM, Mexico City, Mexico, Natl. Autonomous Univ. of Mexico, Mexico City, Mexico; ²Dept. of Psychobiology and Neuroscience, Fac. of Psychology UNAM, Mexico City, Mexico, Univ. Nacional Autonoma De Mexico, Mexico city, Mexico; ³Independent Researcher, CDMX, Mexico

Abstract: Language comprehension engages a left-lateralized dorsal stream and a bilateral ventral stream, but also extends to non-classical regions such as the cerebellum. fMRI studies report co-activation between cerebellar and cortical language areas, suggesting intrinsic connectivity. Right Crus I/II are frequently linked to semantic processing, with emerging

evidence implicating left Crus as well. Clarifying the bilateral role of Crus I and II is essential to mapping a more complete functional architecture of semantic processing. This study examined resting-state functional connectivity between bilateral Crus I/II and semantic ROIs, and assessed their relationship with action fluency performance. Ninety-eight healthy Spanish-speaking adults (54 women; $M = 23.45$, $SD = 3.63$) underwent a 10-minute resting-state fMRI scan followed by an action fluency task. Twenty-five semantic ROIs were identified via Neurosynth meta-analysis ($FDR = 0.01$), and cerebellar Crus I/II were segmented using the multi-atlas segmentation tool CERES. Functional connectivity was assessed using a ROI-to-ROI approach in CONN Toolbox v22. Graph-theoretical metrics were then computed: node strength, degree, and mean connection weight. All four bilateral Crus I and II regions showed connectivity with semantic ROIs. Bilateral Crus I exhibited connections across dorsal, ventral, and extended language comprehension streams, while Crus II regions connected only with ROIs of the dorsal pathway and extended pathway. The highest node strength values were observed for bilateral Crus I (right: 1.162; left: 1.251) with contralateral ROIs, and right Crus I with contralateral ROIs showed the highest node degree (7). Right Crus II showed the highest average connection weight with ipsilateral ROIs (0.2740). Two specific connections from left Crus II—to the right lateral occipital cortex and right frontal pole—emerged as significant negative predictors of action verbal fluency (Estimates: -14.91 and -12.49, respectively). These findings suggest that the intrinsic functional architecture of semantic processing at rest is lateralized, yet symmetrically distributed across cerebellar hemispheres, with right Crus I showing higher node degree with contralateral ROIs and left Crus II exhibiting predictive connections with extended-pathway regions. Moreover, differences between Crus I and II were evident in pathway engagement and network metrics, indicating distinct contributions within the cerebellum.

Disclosures: J. Delerín-Cortés: None. A. Reyes Aguilar: None. E.A. Morales: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.16/MM8

Topic: I.11. Language

Support: NIH Grant R01DC018295

Title: Neural correlates of statistical learning in children with Developmental Language Disorder

Authors: *K. B. BLACK^{1,2}, Z. CAO², A. GUL², K. RABON², J. GOODEN², P. JAIN², L. S. BARON², Y. ARBEL²;

¹Massachusetts Gen. Hosp. - Inst. of Hlth. Professions, Charlestown, MA; ²Communication Sci. and Disorders, Massachusetts Gen. Hosp. Inst. of Hlth. Professions, Boston, MA

Abstract: Developmental Language Disorder (DLD) is a neurodevelopmental condition characterized by difficulties in acquiring and processing language with long lasting effects on

education and quality of life. While the etiology of DLD remains unknown, there is ample evidence that implicit and statistical learning—the ability to extract regularities from sensory input—is affected in DLD. While implicit learning occurs naturally and unconsciously, the impact of explicit strategies on this process remains unclear, particularly in children with DLD. We examine whether suppressing explicit learning mechanisms affects implicit learning in children with DLD compared to typically developing (TD) peers. Children aged 7-12 years with (n=34) and without DLD (n=90) completed an Artificial Grammar Learning (AGL) task, designed to emulate to some extent aspects of language learning. Participants were randomly assigned to a suppression (S) or non-suppression (NS) condition; those in the Suppression condition repeated a syllable (e.g., “key”) during exposure to the artificial language exemplars to suppress the use of phonological rehearsal or inner speech, while those in the No Suppression condition were exposed to the exemplars without the suppression of explicit mechanisms. A test that evaluates the ability to distinguish between grammatically correct (that abide by the structure of the artificial language) and incorrect (violated the structure of the artificial language) strings was presented to all participants. Electroencephalography data collected during testing were analyzed to evaluate the P600 ERP component which is associated with the detection of grammatical rule violations and the N400 component which is linked to semantic processing. Preliminary behavioral data indicate that children with and without DLD met or surpassed the threshold for learning ($>.25$). Preliminary analysis indicates some potential differences in accuracy across groups (TD, DLD) and conditions (suppression, no suppression), with some indications that the suppression condition interfered with learning in the TD group but not in the DLD group. Children with DLD performed slightly better under the suppression condition ($x=0.52$, $SD=0.06$) than no suppression ($x=0.49$, $SD=0.07$), whereas TD children performed slightly worse under suppression ($x=0.50$, $SD=0.08$) than no suppression ($x=0.53$, $SD=0.08$). Preliminary analysis of electrophysiological data also point to potential differences between groups and conditions. Results of the study have the potential to inform researchers and interventionists on whether children with DLD learn better when explicit learning is suppressed.

Disclosures: **K.B. Black:** A. Employment/Salary (full or part-time): Full time. **Z. Cao:** A. Employment/Salary (full or part-time): Full time. **A. Gul:** A. Employment/Salary (full or part-time): Full time. **K. Rabon:** A. Employment/Salary (full or part-time): Part-time. **J. Gooden:** A. Employment/Salary (full or part-time): Full time. **P. Jain:** A. Employment/Salary (full or part-time): Part time. **L.S. Baron:** A. Employment/Salary (full or part-time): Full time. **Y. Arbel:** 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.; PI.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.17/Web Only

Topic: I.11. Language

Title: Abstractness and neuroplasticity

Authors: *M. ORKODASHVILI;
Vanderbilt Univ., Tbilisi, Georgia

Abstract: The research studies the recognition of abstract nouns. The study discusses the development of higher brain plasticity in the process of understanding, explaining and recognizing abstract concepts, metaphors and figurative expressions. What are the main features that differentiate concrete concept comprehension from abstract word / phrase comprehension? Is the abstractness associated with higher executive control and hence, higher brain plasticity? It is assumed that transferring, explaining and understanding an abstract concept across languages is more difficult than transferring, explaining and understanding concrete concepts (i.e. concrete nouns). Especially multilingual and bilingual individuals commonly encounter this challenging task of understanding and explaining abstract concepts in different languages which usually requires elaborate mental activity. As a result of this systematic mental exercise, bilingual and multilingual individuals develop three important advantageous features of cognitive capacity as opposed to monolinguals: 1) quicker response time to understanding abstract concepts; 2) multitasking ability of understanding and reacting (or proacting) to simultaneous multiple tasks such as simultaneous translation and interpretation; and 3) quicker context anticipation. The study so far has come to the following findings: a) bilinguals and multilinguals are 85-95 milliseconds quicker in recognizing and understanding non-literal meanings as opposed to monolinguals; b) monolinguals are 45-55 milliseconds quicker understanding complex texts after being exposed to the metaphoric expressions for a while; c) subjects who have been exposed to metaphoric expressions and texts report the ability of performing two tasks at a time such as simultaneous translation in multiple languages more often than those who have not been exposed to such non-literal expressions; d) furthermore, in the process of reading a new text, the subjects who have been exposed to metaphoric expressions, anticipate the subsequent words, actions or concepts from the context with 78 % precision, as compared to those who have not been exposed to such expressions and who reveal only 22 % precision of anticipation.

Disclosures: M. Orkodashvili: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.18/MM9

Topic: I.11. Language

Title: Communicative Development in Hospitalized Children: The Impact of Intensive Care and Orotracheal Intubation

Authors: *C. P. PIEMONTE¹, F. JUSTE², C. F. D. ANDRADE³;

¹Speech-Language Pathologist, Univ. of Sao Paulo, Sao Paulo, Brazil; ²Univ. of São Paulo, São Paulo, Brazil; ³Univ. of São Paulo, SAO PAULO, Brazil

Abstract: Introduction: Early language development is a dynamic process shaped by neural maturation and enriched through social interactions. The neonatal period is particularly critical, as auditory and somatosensory feedback mechanisms lay the foundation for speech and language acquisition. However, prolonged hospitalization during this sensitive phase, especially in intensive care, can disrupt developmental trajectories. Children with chronic conditions and extended hospital stays are at increased risk for language delays, with preterm infants being particularly vulnerable due to reduced sensory and linguistic input in NICUs. Aim: To evaluate the effects of hospitalization setting (ICU, step-down unit, general ward) and orotracheal intubation duration on the communicative development of children with congenital heart disease. Methods: A prospective, longitudinal, observational study was conducted at the Instituto do Coração - HCFMUSP, with 95 children aged 0 to 5 years and 11 months. Communication development was assessed using the Protocol for Observing Communication Development (POD), which covers auditory-linguistic reception, expressive language, and oral-motor/feeding skills. Scores were converted to percentages and categorized into quartiles (Q1 to Q4). The Shapiro-Wilk test was used to verify normality, and group comparisons were performed using the Kruskal-Wallis test. Results: Children hospitalized in the ICU had significantly lower communicative scores than those in general wards ($p = 0.0007$), particularly in the area of expressive language. No significant association was found between intubation duration (<48 hours vs. >48 hours) and communication outcomes ($p > 0.05$). These results suggest that environmental and affective deprivation in intensive care may be more detrimental to communication than the procedures themselves. Expressive language, which is highly dependent on social reciprocity, emerged as the most affected domain, echoing the literature that highlights the protective role of caregiver-child interaction. Conclusion: ICU hospitalization has a negative impact on early language development, particularly in terms of expressive skills. Environmental deprivation appears to outweigh procedural invasiveness, highlighting the need for early communicative support and humanized care practices in pediatric hospital settings.

Disclosures: C.P. Piemonte: None. F. Juste: None. C.F.D. Andrade: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.19/MM10

Topic: I.11. Language

Support: CEPID NeuroMat - FAPESP 2013/07699-0
SPEC - FAPESP 2018/18900-1
FAPESP Grant 2023/17520-9
FAPESP Grant 2025/00861-3

Title: Bridging brain surgery and electrophysiology: ECoG and language assessment during awake brain tumor surgery - A Case Study

Authors: *P. S. CAMARGO^{1,2}, G. DE OLIVEIRA SANTOS SOUZA⁴, L. ANGELIN¹, A. F. HELENE¹, A. FLINKER^{3,2}, A. L. AREVALO⁵, G. LEPSKI^{4,6};

¹Univ. of São Paulo, São Paulo, Brazil; ²Tandon Sch. of Engin., ³Neurol., New York Univ., New York, NY; ⁴Univ. of São Paulo Med. Sch., São Paulo, Brazil; ⁵Univ. of São Paulo Med. Sch., Sao Paulo, Brazil; ⁶Neurosurg., Eberhard Karls Univ., Tübingen, Germany

Abstract: Functional language assessment during awake brain tumor surgery is essential for identifying cortical areas to be preserved. However, current protocols are often extensive, increasing surgical time and the risk of complications. To address this, we developed the Mini-Intraoperative Language Test (MILT), a brief language battery (originally developed in Brazilian Portuguese) integrated with a value-based decision scale to guide resection of language-related areas. MILT supports the development of an aphasia risk scale and establishes a map correlating stimulated cortical regions with specific language deficits, serving as a guide for future surgeries. Intraoperative electrocorticography (ECoG) complements this approach by enhancing language mapping accuracy, reducing surgical time, and minimizing postoperative aphasia risk. We present a case study of a 64-year-old man with glioblastoma in the left superior frontal gyrus. Surgery was performed under local anesthesia to allow language monitoring. Due to a history of epileptiform activity, direct cortical stimulation was avoided. Instead, a 128-channel ECoG grid recorded language-related neural signals. Preoperative MILT assessment showed largely preserved functions. A mild deficit was observed in verbal fluency (FAS = 1/4), suggesting difficulty with spontaneous lexical retrieval and executive control. The patient showed difficulty generating words based on semantic and phonemic cues within a limited time frame, suggesting mild executive dysfunction in language production. Intraoperatively, three MILT versions (MILT 1 = 37; MILT 2 = 39; MILT 3 = 36) were applied alongside three ECoG grid placements to ensure spatial coverage of language-related signals. No language disturbances were observed, allowing safe resection. Preliminary ECoG analysis revealed task-related high gamma activity in expected regions, supporting MILT's utility in enhancing intraoperative language mapping and improving surgical outcomes.

Disclosures: P.S. Camargo: None. G. de Oliveira Santos Souza: None. L. Angelin: None. A.F. Helene: None. A. Flinker: None. A.L. Arevalo: None. G. Lepski: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.20/MM11

Topic: I.11. Language

Support: Joan Orpella Start-up Funds Georgetown University, Department of Neuroscience

Title: Neural Dynamics Of Stuttered Versus Fluent Speech

Authors: *N. KUMAR, J. ORPELLA;
Georgetown Univ. Med. Ctr., Georgetown, DC

Abstract: Stuttering is a neurodevelopmental communication disorder that affects approximately 80 million individuals worldwide. It is characterized by involuntary disruptions in speech fluency, such as sound and syllable repetitions, prolongations, and articulatory blocks. Accumulating evidence implicates dysfunction within the basal ganglia-thalamocortical (BGTC) loop—a cortico-subcortical network critical for the initiation and temporal sequencing of speech motor programs- as a central mechanism underlying stuttering. However, the precise neurophysiological pathways through which BGTC dysfunction contributes to speech disfluency remain poorly understood. In the first part of this study, we examined functional connectivity during the planning phase of consequent stuttered versus fluent speech using magnetoencephalography (MEG) data previously collected by the senior author (Orpella et al., 2024; Neurobiol Lang). The dataset includes recordings from 31 adults who stutter (8 female; mean age = 30.1, SD = 7.8). To evoke a balanced number of fluent and stuttered speech, participants were first interviewed to identify words they anticipated stuttering on; these words were then embedded into prompts presented during the MEG session. Each prompt required a spoken response containing one of the anticipated words. Source localization was performed using frequency-specific Dynamic Imaging of Coherent Sources (DICS), allowing reconstruction of neural activity and estimation of phase-based connectivity within key speech-related regions. Results revealed atypical connectivity profiles among sub-cortical and cerebellar regions during speech planning for stuttered versus fluent speech that scaled with their Stuttering Severity Instrument-4 metric. The findings suggest fundamental differences in speech-motor network dynamics for subsequently stuttered speech that exist even before speech execution. We then extend these findings in a new study comparing network dynamics during resting state, speech planning, and overt production, specifically examining stuttered and fluent trials within individuals who stutter, as well as fluent speech trials between in adults who stutter and typically fluent controls. This analysis aims to further delineate the atypical functional architecture of the speech-motor system in stuttering.

Disclosures: N. Kumar: None. J. Orpella: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.21/MM12

Topic: I.11. Language

Title: Alexia with agraphia following focal brain lesions in English, Arabic, and Japanese aphasics: implications for the underlying neural network

Authors: *V. BALASUBRAMANIAN;

Communication Neurosci. and Aphasia Res. Lab., Seton Hall Univ., 340 Kingsland Street,
Nutley, NJ

Abstract: Introduction. A recent systematic scoping review of the syndrome of alexia with agraphia (AWA) disclosed multiple lesion sites, and the associated symptom complex in English aphasics (Balasubramanian et al, 2023). An important question to be asked, in this context, is this: Does AWA syndrome occur following multiple sites of lesions across languages/scripts? The phonology-orthography relation in English is somewhat like the one in Arabic, and quite dissimilar to that of Japanese which has phono-syllabic (Kana) as well as whole word writing systems (Kanji) that makes it unique. A comparative study of AWA in English, Arabic and Japanese speakers might offer new insights into the nature of the neural interface between oral reading and writing. Method. A cross-linguistic, case-series analysis of AWA cases with English, Arabic and Japanese background was undertaken. Subjects. A total of 12 AWA cases, (six English, Six Arabic) were included in this study. For Japanese, we could only use previously published case reports while planning to undertake a field study in Japan is underway. Procedure: Analyses of the sites of lesions (brain images) associated with AWA syndromes and characteristics of alexia-agraphia combination in each case. For the identification of AWA characteristics, the Psycholinguistic Assessment of Language Performance in Aphasia (PALPA oral reading and writing subtests) and its equivalent in Arabic were administered to the subjects. Symptom description for Japanese cases was taken from published work. Basic clinical neuropsychological. evaluation of the AWA cases was completed. Results and conclusions: Multiple lesion sites were identified for both English and Arabic AWA cases. Multiple lesion sites support the view that the components of the neural circuitry that subserve the interface between reading and writing are spatially distributed, well beyond the perisylvian area, and include thalamus and cerebellum. It is noteworthy, in this context, that a neuropsychiatric condition can be associated with varying sites of lesions, thereby aiding the discovery of the neural network underlying the pathology (Boes et al, 2015). The data from Japanese AWA cases are very limited. AWA for Kanji is reported following left hippocampal and left posterior inferior temporal cortex hyper perfusion (Maeda & Ogawa, 2011., Sakurai et al, 2008). Further studies, using appropriate imaging methods, might throw more light on the influence of writing systems on the interface between reading and writing.

Disclosures: V. Balasubramanian: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.22/MM13

Topic: I.11. Language

Support: Language in Interaction Synergy Grant from Netherlands Organisation for Scientific Research

Title: Typical oscillatory dynamics in language processing among verbally proficient autistic adults

Authors: *B. STANISLAV, A. STOLK;
Dartmouth Col., Hanover, NH

Abstract: Language delays are often implicated in the developmental trajectory of autism, and prior neuroimaging studies have reported atypical activation patterns during language processing in autistic individuals, particularly in children or those with lower verbal abilities. However, many autistic individuals ultimately attain typical language proficiency. This raises the question of whether the neurophysiological mechanisms supporting language processing differ systematically in autism once language proficiency has been achieved. In this study, we examined brain oscillatory dynamics during language processing in verbally proficient autistic and non-autistic adults. Participants read sentences and pseudoword lists while electroencephalography (EEG) recorded neural activity across the theta, alpha, beta, and gamma frequency bands. Spatiotemporal dynamics during sentence processing were widespread and frequency-specific, including distinct lateralization patterns in the theta, alpha, and beta bands. Additionally, beta-band activity progressively increased as sentences unfolded, reflecting cumulative linguistic processing. Importantly, statistical analyses demonstrated that oscillatory patterns reliably distinguished sentence from pseudoword processing yet were comparable across both groups. Convergent decoding analyses further supported the conclusion that sentence-level language processing unfolds similarly in verbally proficient autistic and non-autistic adults. These findings challenge the notion that language processing is uniformly altered in autism and suggest that previously observed group differences may instead reflect factors influencing language acquisition, rather than differences in language processing once proficiency has been attained.

Disclosures: B. Stanislav: None. A. Stolk: None.

Poster

PSTR048: Language: Acquisition, Usage, and Disorders

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR048.23/MM14

Topic: I.11. Language

Title: Does the Use of a Speech Interpreter Affect Neuropsychological Assessment?

Authors: *A. MARTIN¹, S. TORRES², D. TRANEL³;

¹Neurol., The Univ. Of Iowa, Iowa City, IA; ²Univ. of Iowa Hosp. & Clinics, Coralville, IA, ;

³Dept Neurol, Univ. of Iowa, Iowa City, IA

Abstract: In the United States, 67.86 million people speak a language other than English at home. While many of these homes speak English in addition to the non-English home language, fluency in English is not ubiquitous. A sizable 25.70 million people (8% of the U.S. population)

report speaking, reading, or writing English “less than well” or “not at all.” These individuals are referred to as Limited English Proficiency (LEP) speakers and often need speech interpreters in healthcare and human service settings. When a speech interpreter is used during neuropsychological assessment, the typical dyadic clinician-patient interaction becomes a triadic clinician-interpreter-patient interaction. Interpreter-mediated assessments are common in neuropsychological practice, although the field generally agrees that this is not an optimal approach to assessment of LEP patients. To date, no study has directly evaluated the effect of interpreter use during neuropsychological assessment. To address this, we evaluated test scores and clinical impressions from interpreter-mediated neuropsychological assessments conducted at the University of Iowa Hospitals and Clinics. It was hypothesized that the use of an interpreter would adversely affect neuropsychological assessment. We compared ~120 Spanish-dominant LEP patients tested with a speech interpreter (Group 1) to ~240 demographically and diagnostically matched, fluent English-speaking patients tested without an interpreter (Comparison Group 1). Matching procedures and scoring were independently verified by two raters. The sample ranged in age from 19-92 and included both male and female patients. An additional ~25 Spanish dominant LEP patients tested by fluent Spanish-speaking clinicians (Group 2) were compared to ~50 Comparison Group 2 patients. Preliminary results indicate that: (1) Group 1 performed significantly lower on neuropsychological tests than the Comparison Group 1; (2) Group 1 showed significantly greater variability in test scores; and (3) neuropsychologists’ interpretations of Group 1 assessments were significantly less definitive. Preliminary results from Group 2 suggest that: (1) Group 2 did not perform significantly lower than the Comparison Group 2; (2) Group 2 did not exhibit increased variability in test scores; and (3) assessment interpretations were not less definitive. Overall, these findings provide strong empirical support for the conclusion that interpreter-mediated neuropsychological assessment is not an optimal approach to assessing patients with LEP, and whenever possible, patients should be tested by a provider who is fluent in the patient’s preferred language.

Disclosures: A. Martin: None. S. Torres: None. D. Tranel: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.01/MM15

Topic: J.03. Anatomical Methods

Title: Scalable representation learning for multi-resolution volumetric light-sheet microscopy with a volumetric masked autoencoder framework

Authors: *G. SCHAU¹, C. LAITON², S. SESHAMANI³, D. FENG³, G. HUYNH³;

¹The Allen Inst., Seattle, WA; ²Allen Inst. for Neural Dynamics, Seattle, WA; ³Allen Inst., Seattle, WA

Abstract: Understanding cellular and anatomical structures in large-scale volumetric microscopy data demands scalable, generalizable representation learning techniques that operate effectively across diverse imaging platforms and resolutions. Such datasets, often spanning teravoxels and multiple spatial scales, present significant challenges for both computational throughput and cross-modal generalization. In this work, we introduce NeuroBase, a modular and extensible framework for training transformer-based 3D masked autoencoders (MAEs) on petabyte-scale neuroimaging datasets. Our models are trained in a distributed self-supervised learning environment applicable across imaging platforms that vary in spatial resolution, signal characteristics, and acquisition protocols. We evaluate our approach on multiple public datasets spanning four light-sheet microscopy platforms, including datasets from spatial transcriptomics, whole-brain imaging, and subcellular protein imaging. Each platform contributes unique imaging artifacts and spatial scales, testing the robustness of our learned representations. We assess the learned representations through both qualitative visualization and quantitative metrics. UMAP projections of the model's latent space reveal clustering patterns that correspond to both technical imaging platform and biological content, suggesting the embeddings retain modality-relevant and anatomy-specific signal. Linear classification probes confirm that the features support downstream discriminative tasks, despite being learned via self-supervision. Reconstruction fidelity is measured using per-patch PSNR and mean absolute error (MAE), with high consistency across platforms and resolution tiers. The modular design supports integration of new model variants, datasets, loss functions, and evaluation pipelines, making it suitable for a range of downstream tasks including registration, segmentation, atlas alignment, and morphological phenotype discovery. Because all experiments are fully defined through version-controlled Hydra configs, Neurobase promotes reproducible machine learning for neuroscience, supporting both open science and internal benchmarking workflows, and delivers a critical step toward unifying siloed analyses in computational neuroanatomy.

Disclosures: G. Schau: None. C. Laiton: None. S. Seshamani: None. D. Feng: None. G. Huynh: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.02/MM16

Topic: J.03. Anatomical Methods

Support: NIH Grant R01AR083365

Title: Clearing-enabled light sheet microscopy as a novel method for three-dimensional mapping of innervation in the mouse intervertebral disc

Authors: *D. WILLIAMS¹, S. LEE¹, S. J. THOMPSON¹, M. ALSHAGAWI¹, A. KAUFFMAN¹, L. VULCHANOVA², L. S. STONE^{1,2};

¹Anesthesiol., ²Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Understanding the anatomy of healthy and degenerating intervertebral disc (IVD) innervation is crucial for deciphering the mechanisms of discogenic low back pain. While increased innervation has been linked to back pain, traditional 2D histology provides only a fragmented view of the delicate nerve networks in and around the disc. We leveraged tissue clearing, genetic labeling of sensory neurons, and the SPARC-null mouse model of progressive age-dependent disc degeneration to characterize lumbar disc innervation in 3D. SPARC-null mice were crossed with a Pirt-Cre;Ai14 reporter line to fluorescently label sensory neurons and the SPARC-null/Pirt/Ai14 mice were allowed to age to 12-months. This approach enables visualization of sensory innervation in healthy and degenerated discs without additional staining. Following perfusion and fixation, we obtained high-resolution ex vivo MRI scans of the lumbar spinal column using an Aspect M5TM MRI system and graded lumbar IVDs based on signal intensity: white discs are highly hydrated and healthy, grey discs represent intermediate degeneration, and black discs indicate advanced degeneration. A subset of black discs showed visible herniations and were grouped as a separate phenotype. Discs were dissected, decalcified, and processed using the SmartBatch+ active clearing system (LifeCanvas), incorporating Shield fixation and refractive index matching to preserve fluorescence and tissue integrity. Cleared discs were imaged using single-channel microscopy (RS-G4) and post-processed with a stitching and denoising pipeline implemented on the Minnesota Supercomputing Institute's High Performance Computing system. This clearing approach enabled intact disc imaging with sufficient resolution to reveal sensory axonal networks in and around the discs and adjacent vertebrae. Ongoing efforts will focus on computational quantification of innervation density and relationships between innervation and degeneration severity. This method enables high-resolution mapping of IVD innervation and may offer new insights into how sensory neurons may contribute to disc degeneration and the pathophysiology of back pain.

Disclosures: D. Williams: None. S. Lee: None. S.J. Thompson: None. M. Alshagawi: None. A. Kauffman: None. L. Vulchanova: None. L.S. Stone: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.03/MM17

Topic: J.03. Anatomical Methods

Support: NIMH SBIR Grant R44MH119989

Title: Easy-to-use tools for cleared tissue light sheet image analysis

Authors: J. G. ZEITOUN¹, A. G. REKSOATMODJO¹, C. REDD¹, R. AZEVEDO^{2,1}, *S. P. GANDHI^{2,1}, D. G. WHEELER^{1,3}, P. CHEUNG¹;

¹Translucence Biosystems, Irvine, CA; ²Univ. of California, Irvine, CA; ³Activity Signaling, LLC, San Diego, CA

Abstract: Recent advances in optical clearing and light sheet imaging have opened an exciting new avenue for brain-wide, cellular resolution immunostaining at the forefront of a dimensional shift from 2D to 3D histology. Traditional histological methods have been a mainstay of neuroscience research dating back more than 100 years. Yet, despite great advances in tissue labeling and imaging technology, until very recently imaging more than a few hundred microns into a tissue has required slicing and mounting on slides. When looking for read-outs of genetic or pharmacological manipulations that affect the entire brain, this traditional focused approach is lacking, forcing researchers to limit observations to brain regions of interest. Tissue clearing overcomes these limitations by providing access to the intact brain, offering comprehensive and unbiased anatomical and functional insights. However, these powerful techniques generate terabytes of high-resolution volumetric data per experiment, creating challenges in data processing, reproducibility, and scalability. To address this, we have generated a suite of new tools designed to streamline and disseminate whole-brain image analysis capabilities. This poster extends our previous work and covers Stitchy, Brainseeker, Maverick and Voxels - all designed to simplify whole-brain light sheet image analysis to make this technology accessible to all neuroscientists. Stitchy provides user-friendly automated and adjustable image tiling and stitching for all major light sheet image formats, and now supports batch processing, improved memory management, and z-plane adjustments across fluorescence channels, enabling more efficient large-scale image workflows. Brainseeker is an easy-to-use brain registration tool incorporating standard registration tools like Elastix and ANTs as well as novel AI-based registration tools, registering to the Allen Reference Brain and custom light sheet image reference brains. Maverick facilitates intuitive training and tuning of machine learning-based quantification pipelines. Finally, Voxels is a no-code, drag-and-drop workflow builder that enables researchers to rapidly design and run complex image analysis pipelines, with real-time parameter tracking and visualization across multiple environments, powered by a flexible Kubernetes-based framework. Together, these tools support our mission of empowering scientists to transform large-scale 3D imaging datasets into actionable, reproducible scientific insights.

Disclosures: J.G. Zeitoun: None. A.G. Reksoatmodjo: None. C. Redd: None. R. Azevedo: None. S.P. Gandhi: None. D.G. Wheeler: None. P. Cheung: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.04/MM18

Topic: J.03. Anatomical Methods

Title: Imaging across scales from millimeters to single-digit nanometer resolution

Authors: *M. VELASCO, J. MATTHIAS, C. WURM;
Abberior Instruments America LLC, Bethesda, MD

Abstract: In fluorescence microscopy, target structures of neuroscience samples vary in size, from millimeters in the case of whole organisms or tissues to a few nanometers for single molecules. So far, there hasn't been a microscope available that could provide seamless imaging across this resolution range. The MIRAVA POLYSCOPE by *abberior instruments* addresses this need. It is the first instrument integrating four pivotal microscopy techniques - confocal, MATRIX, STED, and MINFLUX - into a single platform. Key features of the MIRAVA POLYSCOPE include confocal imaging with state-of-the-art features for multiplexing and imaging with optimized photon budget. The MATRIX array detector provides resolution beyond the diffraction limit with full spectral flexibility while minimizing background noise and maximizing signal clarity. Stimulated emission depletion (STED) allows super-resolution microscopy down to 20 nm in 2D and 75 nm in 3D, revealing details of subcellular structures unattainable with diffraction-limited confocal microscopy. And the MINFLUX module enables highly photon-efficient single molecule localization with a precision of down to 3.2 nm. Further modules are designed to overcome challenges of specific applications. Imaging in deep and complex tissues (as is prevalent in neuroscience applications) is facilitated by RAYSHAPE aberration correction. RAYSHAPE relies on a deformable mirror to dynamically correct for aberrations even deep in complex samples, preserving signal and resolution. Adaptive illumination with FLEXPOSURE limits the light dose to the sample, facilitating long-term and volumetric imaging. Fluorescence lifetime imaging is available with TIMEBOW, expanding options for multiplexing and providing additional structural information. TIMEBOW STED exploits the spatial information encoded in fluorescence lifetime to boost image resolution, and may be combined with MATRIX for best results. Intelligent deconvolution with TRUESHARP removes noise and background and enhances resolution by, e.g., incorporating experimentally measured information from MATRIX and TIMEBOW. All these technologies can be easily applied with the intuitive LIGHTBOX software that guides users from initial setup to advanced imaging procedures. The MIRAVA POLYSCOPE combines this user-focused approach with cutting-edge technology for highest robustness and optical quality. It is also future-proof as the modularized hardware simplifies the installation of new components in the field. Taken together, the MIRAVA POLYSCOPE is the all-in-one solution for advanced exploration of biological samples across scales and applications.

Disclosures: **M. Velasco:** A. Employment/Salary (full or part-time): Abberior Instruments America LLC. **J. Matthias:** A. Employment/Salary (full or part-time): Abberior Instruments America LLC. **C. Wurm:** A. Employment/Salary (full or part-time): Abberior Instruments America LLC, Abberior Instruments GmbH. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Abberior Instruments America LLC, Abberior Instruments GmbH.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.05/NN1

Topic: J.03. Anatomical Methods

Support: ERC Synergy Grant No. 951275
NIH R01AG087374
NIH 1R01EB024261
Open Philanthropy
Jed McCaleb
James Fickel
Ashar Aziz

Title: Billion-fold volumetric expansion enables sub-molecular resolution imaging

Authors: *H. HU¹, A. SHAIB³, D. KRAH³, K. RANI³, S. RIZZOLI³, E. S. BOYDEN²;
¹Biol. Engin., ²MIT, Cambridge, MA; ³Univ. of Goettingen Sch. of Med., Goettingen, Germany

Abstract: This technology is an expandable hydrogel platform that physically magnifies biological specimens up to 1500× linearly, or more than three billion times in volume. It decrowds gel-anchored peptide fragments, while preserving spatial relationships, enabling direct, multicolor imaging of protein structures and interactions using ordinary microscopes. The attainable resolution, using conventional confocal microscopy, scales with the expansion factor. At 100× expansion, lateral resolution reaches ~3 nm and axial resolution ~5 nm, with values of ~6 Å and ~10 Å, respectively, for 500×. The lateral resolution improves by an order of magnitude when the samples are analyzed using ONE microscopy, enabling direct visualization of individual amino acids even with a 50× gel. Validation was performed by imaging peptides (mCLING), proteins (GFP, nanobodies) and cells. All samples were anchored via primary amines, digested with Proteinase K, and expanded in water. Imaging was performed using standard confocal microscopy. mCLING and GFP were subjected to peptide chain labeling, using NHS-fluorescein, while both mCLING and the nanobodies carried other fluorophores. We used nanobodies as nanorulers to validate the homogeneity of expansion factors across the successive iteration rounds. The separation between far-red fluorophores, originally ~4 nm, scaled successfully across different expansion factors. Structural investigations of all of these molecules became feasible. For example, for mCLING, a flexible peptide unresolved by cryo-EM due to its small size and corresponding low EM density, we could obtain images in which all seven lysine residues appeared as discrete, spatially separated features at 500× expansion. This is a marked improvement over previous work (Shaib *et al.*, 2024, doi: 10.1038/s41587-024-02431-9), where only the combined lysine side chains could be visualized. While the current study focused on *in vitro* proteins and peptides, our platform should be applicable to the analysis of protein structures and interactions within intact cells and tissues. Signaling pathways, typically inferred from indirect measurements, could now be directly imaged as nanoscale assemblies of interacting proteins, within preserved cellular architecture.

Disclosures: H. Hu: None. A. Shaib: None. D. Krah: None. K. Rani: None. S. Rizzoli: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NanoTag Biotechnologies GmbH. E.S. Boyden: Other; ESB is an inventor on multiple patents in the space of expansion microscopy, and also a co-founder of a company exploring commercial applications of expansion microscopy.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.06/NN2

Topic: J.03. Anatomical Methods

Support: PsyCoMed (ID: 101086247, DOI 10.3030/101086247)

Title: Normalization methods for immunofluorescence on brain sections

Authors: *S. M. MORARA, Sr.¹, A. ZIPPO²;

¹Inst. of Neurosci., C.N.R. (National Res. Council of Italy), Vedano Al Lambro, Italy; ²Inst. of Neurosci., C.N.R. (National Res. Council of Italy), Vedano al Lambro, Italy

Abstract: Immunofluorescence staining intensity of brain sections can be highly variable hampering quantitative analysis. The variability can arise from artifacts produced by an large variety of factors. The issue is particularly relevant for Multiplexed Tissue Imaging (MTI) technologies. A method to overcome this issue is to normalize images. Existing normalization methods often fail to account for the heterogeneous, right-skewed expression patterns of immunofluorescence data or have a high complexity that burden their usage. We conducted a comparison between easily executable, automated normalization procedures using the free software Fiji. Four mice (C57/Bl6) were perfused under deep anaesthesia (according to the EU Directive 2010/63/UE on animal experimentation), brains dissected, cryoprotected, frozen and cut at cryostat. 10 um thick sections were collected on slides and processed for Iba1 immunostaining (code no. 019-19741, FujiFilm). The analysis of microglia Iba1 immunoreactivity was conducted in the prefrontal cortex by LSM 800 Zeiss confocal microscope with 40x objective. From 2 to 7 images were taken from each animal at the same coronal level. The images were segmented by automatic thresholding and processed for normalization by using the A) the median value of the background signal of each image or B) the median value of the specific signal (i.e., the signal above the threshold). Normalization was carried out by 1) subtracting, to the whole image, the median value of the background of the image and adding the overall median value of the background (median of image medians from the 4 animals) or 2) multiplying by the ratio between the overall median value of the background and the median value of the background of the image or 3) subtracting the median value of the specific signal of the image and adding the overall median value of the specific signal (median of image medians from the 4 animals) or 4) multiplying by the ratio between the overall median value of the specific signal and the median value of the specific signal of the image. All methods decreased the coefficient of variation of the specific signal in each image, albeit at different extent in different images, as well as the coefficient of variation of the specific signal among the different animals. However, caution must be taken as different images can produce opposite results with different methods (in particular if the signal is too low or too high, or if artifacts are present, with bakground ratio multiplication). Thus, the present normalization methods are ease-to-use methods to reduce technical variability in immunofluorescence experiments.

Disclosures: S.M. Morara: None. A. Zippo: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.07/NN3

Topic: J.03. Anatomical Methods

Support: NIMH grant MH108053-01
NIMH grant R44MH116827

Title: A novel workflow for whole-brain analysis in rodents using projected light sheet microscopy and artificial intelligence

Authors: M. FAY¹, P. LANG¹, H.-C. GAO¹, *N. J. O'CONNOR¹, P. AFFATATO², O. HON¹, A. WILSON¹, C. S. GERFEN¹, B. EASTWOOD¹, I. K. LORENZEN¹, C. R. GERFEN³, P. J. ANGSTMANN¹, R. TOMER², J. R. GLASER¹;

¹MBF Biosci., Williston, VT; ²Columbia Univ., New York, NY; ³LNP NIMH, Bethesda, MD

Abstract: Characterizing neuronal connectivity, density, and distribution in whole rodent brains provides insights into the functional organization of brain circuits and their relationships to behavior and pathology. Registering brain images to digital reference atlases enables standardized, brain-wide comparisons across experiments, animals, and laboratories.

Toward this we present our SLICE workflow for imaging and analyzing intact cleared whole rodent brains. Our approach leverages projected light-sheet microscopy¹ (developed by Dr. Raju Tomer at Columbia university as a low-cost, high-resolution light sheet imaging method) and neural networks for brain-to-atlas registration, neuronal population characterization, and regional connectivity mapping.

For data standardization, images and experimental endpoints are mapped to the Allen Mouse Brain Common Coordinate Framework (CCF) for adult mice², the Waxholm Space Rat Brain Atlas for adult rats³, and the developing mouse brain atlas (devCCF)⁴ for developmental murine studies.

Our atlas registration methods employ iterative linear and nonlinear methods, informed by fiducials that refine AI-driven mapping. Additionally, example training sets for cell detection and classification are presented and demonstrate reproducibility and accuracy in large-scale brain mapping and neuronal population analyses.

We maintain open data and brain atlas specifications to facilitate the incorporation of external cellular analyses and novel digital atlases. Our data format adheres to FAIR principles, endorsed by the International Neuroinformatics Coordinating Facility (INCF)⁵, ensuring transparency, accessibility, and standardization for cross-institutional research.

1. Chen, Y., Chauhan, S., Gong, C. et al. Low-cost and scalable projected light-sheet microscopy for the high-resolution imaging of cleared tissue and living samples. Nat. Biomed. Eng 8, 1109-1123 (2024).

2. Wang Q, Ding SL, Li Y, Royall J, Feng D, Lesnar P, Graddis N, Naeemi M, Facer B, Ho A, Dolbeare T, Blanchard B, Dee N, Wakeman W, Hirokawa KE, Szafer A, Sunkin SM, Oh SW,

Bernard A, Phillips JW, Hawrylycz M, Koch C, Zeng H, Harris JA, Ng L. The Allen Mouse Brain Common Coordinate Framework: A 3D Reference Atlas. *Cell* 181, 936-953 (2020).
3. Kleven, H., Bjerke, I.E., Clascá, F. et al. Waxholm Space atlas of the rat brain: a 3D atlas supporting data analysis and integration. *Nat Methods* 20, 1822-1829 (2023).
4. Kronman, F.N., Liwang, J.K., Betty, R. et al. Developmental mouse brain common coordinate framework. *Nat Commun* 15, 9072 (2024).
5. <https://www.incf.org/mbf-file-format-v-40>

Disclosures: **M. Fay:** A. Employment/Salary (full or part-time): MBF Bioscience. **P. Lang:** A. Employment/Salary (full or part-time): MBF Bioscience. **H. Gao:** A. Employment/Salary (full or part-time): MBF Bioscience. **N.J. O'Connor:** A. Employment/Salary (full or part-time): MBF Bioscience. **P. Affatato:** None. **O. Hon:** A. Employment/Salary (full or part-time): MBF Bioscience. **A. Wilson:** A. Employment/Salary (full or part-time): MBF Bioscience. **C.S. Gerfen:** A. Employment/Salary (full or part-time): MBF Bioscience. **B. Eastwood:** A. Employment/Salary (full or part-time): MBF Bioscience. **I.K. Lorenzen:** A. Employment/Salary (full or part-time): MBF Bioscience. **C.R. Gerfen:** None. **P.J. Angstman:** A. Employment/Salary (full or part-time): MBF Bioscience. **R. Tomer:** None. **J.R. Glaser:** A. Employment/Salary (full or part-time): MBF Bioscience.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.08/NN4

Topic: J.04. Physiological Methods

Title: A Novel Protein-preserving Passive Tissue Clearing Approach Using Sodium Cholate and Urea for Whole-organ Imaging

Authors: ***K. KIM**¹, J. LEE¹, S. CHANG²;

¹Seoul Natl. Univ., Seoul, Korea, Republic of; ²Physiol. and Biomed. Sci., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Recent advancements in tissue-clearing techniques have opened new possibilities for non-invasive 3D volumetric imaging of a wide range of biological specimens. Passive tissue-clearing methods use diffusion-based processes to infiltrate clearing reagents into samples without mechanical forces or energy input, aiming to minimize sample disruption while preserving tissue architecture and molecular information. Nevertheless, these methods often rely on sodium dodecyl sulfate (SDS) as a delipidating detergent, which has a risk of causing tissue damage and protein disruptions, thus necessitating the development of a reliable yet accessible approach for passive tissue clearing. Here, to achieve better passive infiltration of clearing reagents while retaining structural integrity, we replaced SDS with sodium cholate (SC) and combined it with urea, and developed OptiMuS-*prime* as a novel passive tissue clearing technique. SC, a non-denaturing detergent with small micelles, enhances tissue transparency

while preserving proteins in their native state, while urea disrupts hydrogen bonds and induces hyperhydration to enhance probe penetration. Through optimization of composition and protocols, we found that OptiMuS-prime enables 3D imaging of immunolabeled neural structures and vasculature networks across multiple rodent organs, including the brain, intestine, and lung. The method demonstrated robust clearing and immunostaining capabilities, particularly for detecting subcellular structures in densely packed organs such as the kidney, spleen, and heart, as well as in postmortem human tissues and human induced pluripotent stem cell-derived brain organoids. Together, OptiMuS-*prime* offers a fully accessible and customizable solution for passive clearing and immunostaining, enabling 3D cellular connectivity analysis across whole organisms without the need for extensive tissue-clearing expertise.

Disclosures: **K. Kim:** None. **J. Lee:** None. **S. Chang:** None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.09/NN5

Topic: J.03. Anatomical Methods

Support: NSERC - BESC D 3-559015-2021
NSERC - RGPIN-2018-06506
NSERC - DGEER-2021-00228

Title: Comparison of immunofluorescence quality of human post-mortem brains fixed with solutions used in gross anatomy laboratories

Authors: ***V. PERREAULT**¹, E.-M. FRIGON¹, A. GÉRIN-LAJOIE¹, D. BOIRE¹, J. MARANZANO^{1,2};

¹Dept. of anatomy, Univ. of Québec in Trois-Rivières, Trois-Rivières, QC, Canada; ²Dept. of Neurol. and Neurosurg., McGill Univ., Montréal, QC, Canada

Abstract: Background Brain banks provide small tissue samples fixed with neutral-buffered formalin (NBF) to neuroscientists, but gross anatomy laboratories could also provide brain tissue fixed with solutions used for dissection, such as a salt-saturated solution (SSS) and an alcohol-formaldehyde solution (AFS). Elderly brains (i.e., from body donation programs) and prolonged fixation exposure to aldehydes are known to enhance tissue autofluorescence (AF), limiting the application of immunofluorescence (IF) staining. Our previous work using IF demonstrated the preservation of antigenicity and absence of AF in mice brains fixed with all three solutions. This study aims to compare the IF staining quality of human brains fixed with solutions used in gross anatomy laboratories (SSS and AFS) vs. NBF-fixed brains (practice of brain banks), and to compare the efficiency of methods employed to quench AF, such as Sudan Black B (SBB) or Sodium borohydride (NaBoro). **Methods** We used a convenience sample of 18 brains (9 males/females; 44-96 years old) fixed with NBF (N=6), SSS (N=6), and AFS (N=6). Blocks of

1cm³ of neocortex were extracted, cryoprotected, frozen, and cut into 40µm sections using a cryostat. All specimens were treated with and without an antigen retrieval (AR) protocol before performing immunofluorescence staining for neurons (anti-NeuN, AlexaFluor 488) and astrocytes (anti-GFAP, AlexaFluor 555) followed by SBB and NaBoro treatments that were used independently. Sections were observed with a spinning-disk confocal microscope with excitation at wavelengths of 488nm, 555nm and 647nm, to assess two variables using qualitative scores: 1-autofluorescence (criteria: background AF and cell AF) and 2-immunostaining quality (criteria: antibody penetration and cell distribution). **Results** Following an AR protocol, brains fixed with all three solutions showed similar antigenicity preservation, which was always excellent for astrocytes, while neurons weren't always preserved. The overall AF intensity was similar in brain sections fixed with all three solutions, and background AF was higher in the 488nm channel. SBB treatment was the most effective at reducing overall AF in all specimens and was needed to make neurons visible in the 488nm channel. **Conclusion** Brains fixed with SSS and AFS could be good alternatives for NBF-fixed specimens, given the similarity of our results from AF and antigenicity assessment. We suggest using SBB treatment to mitigate tissue AF, especially if performing IF staining in the 488nm channel. In the context of IF experiments, these results are promising for neuroscientists aiming to use brains from gross anatomy laboratories.

Disclosures: V. Perreault: None. E. Frigon: None. A. Gérin-Lajoie: None. D. Boire: None. J. Maranzano: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.10/NN6

Topic: J.03. Anatomical Methods

Support: NCATS/NIH I UL1 TR002345 and the McDonnell Center for Cellular and Molecular Neurobiology at WashU Medicine.

Title: A correlated super resolution volume electron microscopy protocol optimized for pediatric brain tumors

Authors: *E. ROSA-MOLINAR¹, D. M. OAKLEY²;

¹Cell Biol. & Physiol. and Neurosci., ²WashU Ctr. for Cell. Imaging, WashU Med., Saint Louis, MO

Abstract: Chromatin organization is key in defining cell transcription during normal cellular processes and development. The mechanical forces that stress cells are seen in their nuclei via the connection of the cytoskeleton and nucleoskeleton directly affect chromatin. Chromatin dysregulation has been implicated in aberrant chromatin organization that can trigger gene expression alterations linked to brain cancer. However, how the genome integrity is protected against mechanically induced stress is unknown. Here, we provide an integrated workflow to

carry out correlated super-resolution volume electron microscopy on pediatric brain tumor tissues obtained from the Washington University Pediatric Neurosurgery Tissue Bank. All subjects consented and were enrolled in the Pediatric Neurosurgery Tissue Bank. Correlated super-resolution volume electron microscopy was used to show the mechanosensitive proteins in the cell's nuclear membrane and allow the three-dimensional (3D) visualization of chromatin and nucleosomes changes in pediatric brain tumor tissue. Correlated super-resolution volume electron microscopy revealed substantial differences and changes in mechanosensitive proteins in the cell's nuclear membrane, chromatin, and nucleosomes between brain tumor and tumor-free tissues. Brain tumor tissues revealed large oblate nuclei with a dramatic increase in their numbers and a reduction in the cytoplasmic area. In conclusion, we hope our in-depth imaging analysis will provide a basis for further understanding the role of mechanical stress in genome integrity and continue investigations that may result in novel strategies for targeted pediatric brain cancer.

Disclosures: E. Rosa-Molinar: None. D.M. Oakley: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.11/NN7

Topic: J.03. Anatomical Methods

Support: UM1NS132207
R01MH126923

Title: Brain imaging with polarization-sensitive optical coherence tomography at visible and near-infrared spectral bands

Authors: *B. BARADARAN¹, H. M. HEINKS¹, M. YEATTS¹, N. CHINTHALAPATI¹, S. R. HEILBRONNER², T. AKKIN¹;

¹Biomed. Engin., Univ. of Minnesota, Minneapolis, MN; ²Neurosci., Baylor Col. of Med., Houston, TX

Abstract: High-resolution, large-volume brain imaging is necessary to advance our understanding of neural function, physiology, and pathology. Despite the significant development of neuroimaging technologies in recent years, there is still a pressing need to establish imaging techniques that can highlight brain structures and fiber pathways. Optical Coherence Tomography (OCT) is a label-free, non-contact imaging method employed in various biomedical applications with a spatial resolution of 1-10 μm . An advanced form of OCT, polarization-sensitive (PS)-OCT, measures tissue birefringence, an optical anisotropy determined by axis-dependent variations in refractive index. Myelin, abundantly found in white matter, exhibits strong birefringence, enabling PS-OCT to effectively delineate myelinated axon fiber bundles when imaging the brain. One of the primary design parameters in a PS-OCT system is

the source wavelength, which can range from visible to near-infrared (NIR) spectra. While NIR PS-OCT offers superior penetration depth and signal-to-noise ratio, visible light PS-OCT provides higher axial resolution and increased birefringence sensitivity (Baradaran et al., 2025). In this study, we compare how imaging at different spectral regions affects PS-OCT contrasts when investigating white and gray matter. A slice of macaque brain tissue containing the thalamus is imaged using both NIR and visible-light PS-OCT systems. PS-OCT contrasts, including reflectivity, attenuation, retardance, and optic axis orientation, are compared between and within the two systems. The results highlight distinct advantages of each spectral band, suggesting that the optimal PS-OCT configuration may be selected based on the specific neuroimaging application.

Disclosures: B. Baradaran: None. H.M. Heinks: None. M. Yeatts: None. N. Chinthalapati: None. S.R. Heilbronner: None. T. Akkin: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.12/NN8

Topic: J.03. Anatomical Methods

Support: NIH Grant U01NS132181
NIH Grant UM1NS132358
NIH Grant R01NS128843
NIH Grant P41EB015896
NIH Grant P41EB030006
NIH Grant R00EB023993
NIH Grant R21HD106038

Title: Imaging 3D fiber orientation and myeloarchitecture of human brainstem with PS-OCT

Authors: N. BLANKE, J. WAN, C. CLICKNER, J. NOLAN, C. MAGNAIN, *H. WANG; Massachusetts Gen. Hosp., Charlestown, MA

Abstract: The accurate measurement of three-dimensional (3D) fiber orientation and myelin content in the brain is crucial for reconstructing fiber pathways and studying their involvement in neurological diseases. Comprehensive reconstruction of axonal tracts and small fascicles requires high-resolution technology beyond the ability of current in vivo imaging (e.g., diffusion weighted magnetic resonance imaging). Optical imaging methods such as polarization-sensitive optical coherence tomography (PS-OCT) can image myelinated fiber tracts at micrometer resolution in the brain. PS-OCT is a label-free volumetric imaging technique that utilizes the optical birefringence of myelin to directly quantify myeloarchitecture and map the in-plane axis of white matter fiber bundles at a resolution of 1-10 μm isotropic. In combination with serial sectioning, the block-face PS-OCT allows volumetric reconstruction of tens to hundreds of cubic

centimeter human brain samples with minimal distortion. In this work we present a novel method to quantify 3D axis orientation and the true birefringence of fiber tracts with PS-OCT in postmortem human brainstem tissues. Volumetric reconstruction of brainstem is achieved at 20 μm isotropic resolution. The 3D axis orientation represents direct fiber orientation, and the true birefringence represents the myelin content in the white matter tracts. We measure the polarization contrasts of the brain sample from two illumination angles of 0 and 15° and apply a computational method that yields the two quantitative maps. We further present a ultra-high resolution 3D fiber orientation and birefringence maps of brainstem, revealing unprecedented details of fiber and nuclei configurations. We envision that our method will open a promising avenue towards understanding large-scale connectivity networks in the human brainstem.

Disclosures: N. Blanke: None. J. Wan: None. C. Clickner: None. J. Nolan: None. C. Magnain: None. H. Wang: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.13/NN9

Topic: J.03. Anatomical Methods

Support: UM1 NS132207

Title: Serial PS-OCT Imaging of a Whole Macaque Brain

Authors: *M. YEATTS;
Univ. of Minnesota, Minneapolis, MN

Abstract: Serial PS-OCT Imaging of a Whole Macaque Brain

Authors MariPen Yeatts¹, Taner Akkin^{1,*}

¹University of Minnesota, Minneapolis, MN Disclosures

M. Yeatts: None. T. Akkin: None.

Abstract

One solution to the problem of mapping mesoscale connections in the brain is the use of serial polarization-sensitive optical coherence tomography (PS-OCT). This technique takes advantage of the naturally occurring birefringent properties of white matter to produce label-free contrasts. The serial design allows for blockface imaging, removing the distortions associated with slide mounting. In previous work, we have demonstrated that this technique is effective in mouse brains and small portions of primate brains. Here, we demonstrate the serial PS-OCT imaging of an entire macaque brain (both hemispheres) at 10 x 10 x 5.5 μm^3 resolution. We overcame multiple hurdles associated with this increased size, including hardware, software, storage, and data processing. This unprecedented mesoscale imaging allows for connectivity and white matter organization analysis of the whole macaque brain. Two datasets have been taken, one complete brain in the coronal plane, and one partial in the sagittal plane. We are currently analyzing the

following PS-OCT contrasts: reflectivity, retardance, and optic axis orientation. Future work includes comparison with dMRI from the same animal, as the optic axis orientation provides a ground truth in areas of fine or crossing fibers.

Disclosures: M. Yeatts: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.14/NN10

Topic: J.04. Physiological Methods

Support: NIH Grant R21OD033664
NIH Grant S10OD032136
Advancing a Healthier Wisconsin Endowment Grant

Title: See-through science: *Danionella cerebrum* as a model for neuroregeneration

Authors: *M. K. MISYUK¹, J. L. AUSTIN¹, N. R. WALECHKA¹, J. A. PETERKA¹, M. B. VELDMAN¹, P. LAM²;

¹Cell Biology, Neurobio. and Anat., ²Neurosci. Res. Ctr., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Rebuilding functional neuronal circuits after injury in the adult central nervous system (CNS) is unachievable for many vertebrates. In pro-regenerative models, it is unclear how regeneration and re-wiring is achieved in the CNS over long distances. The size and opacity of the adult vertebrate brain makes it difficult to study axon topography and dynamic cellular interactions during long-distance axon regeneration. Here, we harnessed the properties of the small and transparent adult *Danionella cerebrum* for longitudinal *in vivo* imaging of retinal ganglion cell axon regeneration, correlating cellular events with functional recovery. Our results suggest that some axons regenerate along tracts of degenerating myelin debris. However, the topography of re-innervation is different after regeneration, suggesting that new axon tracts are created to restore functional vision. The *D. cerebrum* model provides a unique opportunity to visualize and experimentally manipulate the spatial and temporal events during CNS regeneration in intact adult vertebrates.

Disclosures: M.K. Misyuk: None. J.L. Austin: None. N.R. Walechka: None. J.A. Peterka: None. M.B. Veldman: None. P. Lam: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.15/NN11

Topic: J.03. Anatomical Methods

Support: Fisher Center for Alzheimer's Research Foundation
Leon Levy Scholarships in Neuroscience

Title: Whole-brain Cell Mapping with Highly Multiplexed In Situ Hybridization Toward Standardized Neuroanatomy

Authors: *T. MURAKAMI, N. HEINTZ;
The Rockefeller Univ., New York, NY

Abstract: Recent advances in three-dimensional single-cell-resolution imaging have begun to link organ-wide and cellular level research in development and disease research. Harnessing the power of whole-mount cell staining and tissue-clearing, it became possible to quantify the cell populations throughout an intact organ. While powerful, whole-organ imaging remains limited by the inability to stain a broad range of molecular markers simultaneously and by the lack of an analytical scheme to precisely quantify the cell population. Here, we present a highly multiplexed whole-mount staining technique, utilizing the repeated application of fluorescent in situ hybridization. This technique, termed mFISH3D, was designed by extensively dissecting the chemical basis of hybridization reactions in fixed tissue. mFISH3D enabled the visualization of 10 types of mRNAs in an intact mouse brain and has been demonstrated in various biological specimens including the human brain. To achieve previously unattained levels of accuracy in cell mapping, we developed artificial intelligence (AI)-driven workflow using self-supervised learning, significantly reducing the need for extensive manual annotations. To quantitatively analyze postmortem human cerebral cortex, we have reconstructed morphogenic tracks of cortical growth, and used the tracks to provide a framework for assessment of cytoarchitecture. The integration of mFISH3D with our analysis workflow sets a standard for high-dimensional tissue analysis, provides a new systematic framework for analyzing complex cellular ecosystems and enables comprehensive investigation of selective cellular vulnerabilities in diseases.

Disclosures: T. Murakami: None. N. Heintz: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.16/NN12

Topic: J.08. Methods to Modulate Neural Activity

Support: UM1NS132207

Title: High-speed light-sheet microscopy for large-volume axonal tract tracing in the non-human primate brain

Authors: *M. SHOURAV¹, K. TAKASAKI³, A. HELLEVIK³, R. REID⁴, G.-Q. BI⁵, K. UGURBIL⁶, S. R. HEILBRONNER⁷, J. ZIMMERMANN²;

¹Univ. of Minnesota, Saint Paul, MN; ²Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN; ⁴Neural Coding, ³Allen Inst. for Brain Sci., Seattle, WA; ⁵Univ. of Sci. and Technol. of China, Anhui, China; ⁶Neurosci/radiology/biochem/med, Univ. Minnesota, Minneapolis, MN; ⁷Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Understanding long-range axonal projections in the primate brain is critical for unraveling neural circuit organization and connectivity. To address the challenge of imaging large-scale, high-resolution datasets for axonal tract tracing, we developed a MEMS-based oblique iSPIM light-sheet microscope optimized for high-speed volumetric imaging of GFP-labeled whole macaque brain tissue. The system integrates four solid-state lasers (405, 488, 561, 647 nm) directed through a MEMS scanning mirror and relay lenses to generate a scanned light-sheet. The illumination and imaging arms are arranged perpendicularly at a 45° angle relative to the sample surface, using a 4× objective (NA 0.1) for illumination and a 10× objective (NA 0.3) for detection, achieving ~6.85× effective magnification under high-refractive-index conditions (RI = 1.52). Beam profiling in fluorescein solution revealed a ~5.5 μm beam waist and ~428 μm confocal parameter, matching Gaussian beam simulations. The system offers a ~300 μm (Z) × 2000 μm (Y) field of view per frame, with raw voxel sizes of ~0.70 μm (Z), ~0.95 μm (Y), and ~0.97 μm (X), resampled to isotropic 1 × 1 × 1 μm³ for analysis. Point spread function (PSF) measurements using 500 nm fluorescent beads indicated ~1.7 μm lateral and ~9.3 μm axial resolution without deconvolution. We acquired continuous 16-bit volumetric stacks at 200 fps with a 0.5 mm/s stage speed, imaging 300-μm-thick macaque brain slices immersed in refractive-index-matching solution. The system enabled clear visualization of labeled neurons and fine axonal projection paths, demonstrating its capacity for high-throughput, large-scale brain imaging. Together, these results establish our oblique iSPIM platform as a powerful tool for detailed axonal tract tracing and reconstruction of primate brain circuitry.

Disclosures: M. Shourav: None. K. Takasaki: None. A. Hellevik: None. R. Reid: None. G. Bi: None. K. Ugurbil: None. S.R. Heilbronner: None. J. Zimmermann: None.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.17/OO1

Topic: J.04. Physiological Methods

Support: RFINS113287
RFINS1260441
Interdisciplinary Doctoral Fellowship (IDF) , University of Minnesota

Title: Cortex-wide cellular resolution imaging in freely locomoting mice

Authors: *A. CHERKKIL^{1,2}, Z. VIAVATTINE², K. SAXENA², V. KOTA², I. OLADEPO², D. SURINACH³, J. HU⁴, E. KO⁵, J. JUNEAU⁶, S. B. KODANDARAMAIAH⁷;

¹Univ. of Minnesota, Minneapolis, MN; ²Univ. of Minnesota, Twin Cities, Minneapolis, MN;

³Objective Biotech., Minneapolis, MN; ⁴Motif Neurotech, Huston, TX; ⁵Univ. of Minnesota - Twin Cities, Minneapolis, MN; ⁶MIT, Kavli Inst., Massachusetts, MA; ⁷Univ. Of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Recent work using one and two-photon mesoscopes has revealed important insights into how cortical circuits simultaneously coordinate their activity to mediate behavior. This involves recording neural activities from distributed populations of cortical neurons. Imaging large-scale cortical neural activity currently requires large form-factor neural imaging instrumentation, limiting imaging studies to those involving head fixation. Currently, we lack adequate technologies to simultaneously capture cortex-wide cellular activity in moving animals engaging in naturalistic and ethological behaviors. To address this challenge, we have developed the Cortex-CAM (Camera Array Microscope) that integrates four widefield imaging micro-cameras into one compact form factor device for cortex-wide calcium imaging. Each micro-camera is equipped with a pin-hole aperture compound lens capable of imaging over 6.5 x 5.8 mm cortical area at a full-pitch resolution of ~12 μm . The four micro-cameras image slightly overlapping fields of view, collectively imaging a 48mm² area of the dorsal cortex through multi-faceted cranial windows. The Cortex-CAM can capture Ca²⁺ activities of over 6000 neurons with DFF > 50 % in head-fixed transgenic mice sparsely expressing GCaMP6 in layer 2/3 of the cortex. The Cortex-CAM weighs ~49g and can be integrated into a mechanically simple, sliding and rotating head-docking mechanism to realize a mobile Cortex-CAM. Mice head-docked to the mobile Cortex-CAM have volitional control over x and y translation and are free to rotate their heads about the yaw axes. With the weight of the Cortex-CAM fully supported by the sliding and rotation mechanism, mice readily acclimatize to head docking on the mobile Cortex-CAM and can freely explore two-dimensional spatial environments. Mice exhibit a repertoire of complex naturalistic behaviors, including foraging, grooming, and thigmotaxis, and can be trained to perform an alternating choice task with proficiency comparable to freely behaving mice. As a proof-of-concept demonstration, we show recordings of 1000s of neurons distributed across the whole dorsal cortex while the mice perform an alternating choice task.

Disclosures: A. Cherkkil: None. Z. Viavattine: None. K. Saxena: None. V. Kota: None. I. Oladepo: None. D. Surinach: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Objective Biotechnology. J. Hu: None. E. Ko: None. J. Juneau: None. S.B. Kodandaramaiah: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Objective Biotechnology.

Poster

PSTR049: Light and Electron Microscopy: Large Volume Imaging and Tissue Clearing

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR049.18/OO2

Topic: J.04. Physiological Methods

Support: NIH Grant K25AG086674
CIHR grant 507738

Title: Neuronal Imaging using Incoherent Holographic Lattice Light-Sheet with Phase Mask Optimization

Authors: M. POTCOAVA¹, Z. ZURAWSKI¹, S. SAGOSHI³, I. LU¹, C. MANN⁴, *S. T. ALFORD²;

¹Anat. and Cell Biol., ²Univ. of Illinois, Chicago, Chicago, IL; ³Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL; ⁴Applied Physics and Materials Sci., Northern Arizona Univ., Flagstaff, AZ

Abstract: Light sheet microscopy is a fluorescence imaging technique that illuminates a single plane of the sample, creating a thin optical section. This allows rapid, non-invasive, long-term, imaging of samples, in live organisms. **Lattice light-sheet (LLS) microscopy**, optimizes speed and reduces phototoxicity. It is particularly useful for imaging dynamic processes over extended periods. However, while z-galvanometer mirror scanning of the lattice sheet is rapid for 3D imaging, the emission objective focal plane or the sample stage must be moved. Moving tissue precludes electrophysiology. Moving the objective is slow, it is heavy, and this causes mechanical artifacts. LLS beams are coherent and produce stronger modulation depth than incoherent patterned light sheets but work by causing fluorescence, giving incoherent emitted light. We explore self-interference properties of this fluorescence, in which interference patterns are created with sample depth information encoded in these patterns. This is done using one or two diffractive lenses on a phase modulation SLM in the LLS detection arm while moving the LLS excitation light for optical sectioning. Without objective movement, multiple planes are acquired without loss of temporal resolution or mechanical artifacts. This enables high-speed detection with low-light volumetric imaging available from LLS microscopy. We call this add-on detection system, the incoherent holographic lattice light-sheet (IHLLS) module. Although IHLLS offers high spatiotemporal imaging, use of high laser intensity remains a problem when imaging neurons. To address this, we present a phase mask optimization scheme of one diffractive lens IHLLS (IHLLS-1L), by altering the IHLLS diffractive lens' phase with a randomly selected pixel phase mask without altering the extended FOV offered by previous IHLLS configurations. This mask, positioned at a conjugate plane of the back aperture of the detection objective, shapes further the light collected from the sample before it reaches the camera. It is adjusted together with the diffractive lenses by the galvanometric mirror to improve optical sectioning. To demonstrate the use of this approach we present fluorescent images of the presynaptic structures of hippocampal inhibitory interneurons and of the Ca²⁺ sensor, jRCaMP1a expressed in these interneurons. We show that in aging and APOE4 Alzheimer's disease model mice, the presynaptic Ca²⁺ signal is substantially altered.

Disclosures: M. Potcoava: None. Z. Zurawski: None. S. Sagoshi: None. I. Lu: None. C. Mann: None. S.T. Alford: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.01/OO3

Topic: J.06. Computation, Modeling, and Simulation

Support: NSF FGNM06 Career

Title: A neural uncertainty principle governs identifiability in recurrent network models of neural dynamics

Authors: *A. BERTICS¹, F. DINC³, L. STORAN⁴, N. MIOLANE²;

¹Dynamical Neurosci., ²Dept. of Electrical and Computer Engin., Univ. of California, Santa Barbara, Santa Barbara, CA; ³Kavli Inst. for Theoretical Physics, UC Santa Barbara, Santa Barbara, CA; ⁴Dept. of Applied Physics, Stanford Univ., Stanford, CA

Abstract: Recurrent neural networks (RNNs) are widely used to model neural dynamics from brain recordings as animals perform tasks, and their dynamics are analyzed to generate testable hypotheses about underlying biological circuits. However, distinct RNNs can reproduce the same neural trajectory nearly perfectly while relying on different internal mechanisms. This raises a challenge for interpretability: when are RNNs uniquely constrained by data? To answer this question, we derive formal conditions under which the parameters of an RNN are identifiable from its trajectory and characterize equivalence classes of RNNs that yield identical dynamics despite differing parameters. Our analysis reveals a neural uncertainty principle: the subspace spanned by the observed trajectory constrains linear combinations of parameters. Based on this, we introduce a targeted intervention strategy to disambiguate parameters and validate predictions in noisy simulations of random and task-trained RNNs. These findings offer concrete tools for interpreting and constraining RNN models of neural dynamics.

Disclosures: A. Bertics: None. F. Dinc: None. L. Storan: None. N. Miolane: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.02/OO4

Topic: J.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI 21K15611
JST CREST JPMJCR23N2

Title: Extended Hopfield dynamics with momentum generates hippocampal replay for efficient memory sampling

Authors: *T. HAGA;

Ctr. for Information and Neural Networks, Natl. Inst. of Information and Communications Technol., Osaka, Japan

Abstract: Hippocampus generates replay of activity patterns corresponding to past experiences. Recent theoretical studies suggest that hippocampal replay prioritizes reactivation of episodes that are useful for reinforcement learning, which is called prioritized experience replay (Mattar & Daw, 2018; Diekmann & Cheng, 2023). However, how we can design hippocampal neural network dynamics for prioritized memory sampling, and whether behaviors of such network model are consistent with experimentally observed dynamical properties of hippocampal replay, is not fully understood. Here I propose an extended Hopfield-type attractor network model called momentum Hopfield model. In the momentum Hopfield model, I considered the momentum and corresponding kinetic energy associated with the potential energy of Hopfield-type model, and I assumed conservation of the total energy. I applied this principle to the modern Hopfield model (Ramsauer et al., 2020) and obtained CA3-CA1 network model with internal oscillatory dynamics in CA3 neurons. I demonstrate that this network model can reproduce experimentally observed dynamical properties in hippocampal replay; discrete transitions across a fixed set of activity patterns (“hover-and-jump dynamics”), elongation and slow-down of replay with more experience (increased number of memories), and Brownian-motion-like replay trajectories for familiarized 2-D spaces. Furthermore, I prove that dynamics of the momentum Hopfield model is mathematically equivalent to Monte Carlo sampling from Gaussian mixture, and sampling frequency (mixing ratio) of embedded memories is determined by norms of memory pattern vectors. Using this property, the momentum Hopfield model can be used to implement prioritized experience replay by assuming overrepresentation and increased excitability of place cell activities by dopamine (corresponding to reward or temporal-difference (TD) error). In a simple grid-world setting, I demonstrate that momentum Hopfield model with appropriate memory amplification accelerates value learning for spatial navigation. The momentum Hopfield model provides a theoretically tractable and biologically plausible dynamical framework for prioritized memory sampling in hippocampal replay.

Disclosures: T. Haga: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.03/OO5

Topic: J.06. Computation, Modeling, and Simulation

Title: An analytical framework for determining memory storage capacity of neural networks under competing demands of pattern separation and completion

Authors: *Z. Z. CHOU¹, J.-M. C. BOUTEILLER²;
²Biomed. Engin., ¹USC, Los Angeles, CA

Abstract: Memory systems must balance the conflicting demands of pattern separation and pattern completion, needing to both differentiate between similar patterns and reconstruct full patterns from partial or degraded cues. These processes are thought to be jointly implemented in hippocampal and cortical circuits, yet they impose opposing demands on neural representations and ultimately constrain memory storage capacity. In this study, we investigate how varying the balance between separation and completion impacts the theoretical and practical memory capacity of sparse neural circuits. In this study, we build on prior work that established optimal capacity conditions for pattern sparsity and differentiability to expand on the ideal usage of activation thresholds to govern the allowable overlap between stored patterns. Using a simplified model of a feedforward network with binary units and fixed activation thresholds, we quantify how increasing tolerance for overlap reduces the minimum Hamming distance between patterns, thereby increasing generalizability at the cost of unique recall. Conversely, strict separation constraints increase minimum distances, preserving pattern identity but reducing capacity. We derive closed-form expressions for capacity as a function of separation-completion tradeoff parameters and demonstrate that stored representations can be efficiently reorganized post hoc to shift between these regimes with minimal cost. These results provide an analytical framework for how neural systems may dynamically modulate pattern representation via plasticity or coding strategies in order to optimize memory performance in brain areas involved in episodic and associative memory.

Disclosures: Z.Z. Chou: None. J.C. Bouteiller: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.04/OO6

Topic: J.06. Computation, Modeling, and Simulation

Support: DFG CRC-TRR 384/1

Title: Disentangling Stimulus and Circuit Contributions to Neural Manifolds

Authors: S. GOEDEKE¹, J. KAUTZ², *C. LEIBOLD³;

¹Bernstein Ctr. Freiburg, Univ. of Freiburg, Freiburg im Breisgau, Germany, Freiburg, Germany;

²Uni Freiburg, Freiburg, Germany; ³Univ. of Freiburg, Freiburg i. Br., Germany

Abstract: Neural population activity often exhibits low-dimensional structure, coined as neural manifold, but it remains unclear to what extent this geometry represents stimulus space or local circuit computations. We developed a mathematical framework to dissect feedforward versus recurrent contributions to neural manifold geometry using continuous firing-rate recurrent neural networks (RNNs). Inputs are generated from stimulus manifolds with given geometry via

localized tuning functions, and we systematically progress from uncoupled neurons over low-rank recurrent to random connectivity. We compute Riemannian metrics of resulting neural manifolds and analyze how recurrent dynamics shape geometry, particularly for time-varying inputs modeled as random trajectories on stimulus manifolds. In RNNs with fast stable dynamics, manifold geometry primarily reflects input structure. However, temporal dynamics play a particularly important role when neural time scales match stimulus time scales. Then, input geometry becomes scrambled, increasing the dimensionality of the neural activity manifold beyond the stimulus manifold, suggesting a way to probe higher-dimensional computations. Low-rank connectivity enables selective focusing on stimulus manifold regions, allowing networks to warp specific regions of the stimuli. Our theoretical predictions were confirmed through numerical simulations using local intrinsic dimensionality estimation. These findings demonstrate that temporal dynamics—both of stimuli and circuit time scales—are essential to consider when interpreting experimental neural manifold studies.

Disclosures: S. Goedeke: None. J. Kautz: None. C. Leibold: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.05/OO7

Topic: J.06. Computation, Modeling, and Simulation

Support: Israel Science Foundation Grant 794/22

Title: How mixed connectivity shapes critical transitions in recurrent neural networks

Authors: *A. DOTAN¹, O. SHRIKI²;

¹Cognitive and Brain Sci., Ben-Gurion Univ. of the Negev, Be'er Sheva, Israel; ²Cognitive and Brain Sci., Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel

Abstract: Recurrent cortical circuits are claimed to hover near critical points where small changes in wiring can tip activity from one dynamic regime to another. Real-world connectivity is neither purely random nor perfectly ordered; dense, disordered synapses coexist with low-rank motifs that embed global structure. We examine how this blend of connectivity components governs the type of transition a network encounters.

In rate-network simulations, we varied three statistical features of the recurrent weight matrix independently: (1) average synaptic drive—controls the drift toward uniform runaway activity, (2) random variability—modulates the emergence of high-dimensional chaos, and (3) strength of a single low-rank motif—favors activity that organizes into pattern-like states, even when strong disorder may suppress clear symmetry breaking.

By sweeping these parameters we generate a three-dimensional phase diagram that reveals distinct routes to instability. Preliminary results suggest that different transitions may result in either over-amplification, chaotic behavior, or pattern-formation.

Understanding the effect of recurrent wiring in the brain on the interplay between the different kinds of phase transitions may lead to a better understanding of different critical phenomena in the brain, such as epileptic seizures and hallucinations.

Disclosures: A. Dotan: None. O. Shriki: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.06/OO8

Topic: J.06. Computation, Modeling, and Simulation

Title: Quantifying and Engineering Emergent Dynamics in Biological and Artificial Neural Networks

Authors: *J. LI^{1,2}, S. PARDO GUERRA³, G. A. SILVA⁵, K. BASU⁴;

¹UCSD, LA JOLLA, CA; ²Ctr. for Engineered Natural Intelligence, UCSD, La jolla, CA;

³Bioengineering, UCSD, La Jolla, CA; ⁴Ctr. for Engineered Natural Intelligence, UCSD, LA JOLLA, CA; ⁵Bioengineering, Univ. of California San Diego, La Jolla, CA

Abstract: Understanding how new, system-level properties emerge from interacting neural elements is critical, yet existing metrics are largely phenomenological and provide limited mechanistic insight. We recast emergence as a form of structural non-linearity that can be formalized algebraically. We propose a computable framework that treats biological or artificial neural networks as directed graphs equipped with a lightweight algebraic bookkeeping scheme. By asking how the observable function of the network changes when selected nodes or connections are hidden or pruned, we obtain a single, interpretable score that locates the specific elements most responsible for the newly appearing behavior. Tested across simulated networks with a broad range of connection densities, the score increased in lock-step with classic information-loss metrics, suggesting it captures a core facet of emergence while remaining easy to compute and interpret. Beyond revealing the substrates of emergence in neural systems, the same score can be woven into modern machine-learning pipelines: by deliberately scaling layer weights at initialization so the metric is promoted, deep models start out with more active information-carrying paths, learn more quickly, and settle into flatter, more robust solutions across vision, language, and sequence-learning tasks. Because the method only requires the graph structure plus a user-defined notion of “what is observed,” it naturally scales from micro-circuits to large-scale connectomes and can incorporate factors such as synaptic pruning, imaging resolution, or coarse-grained time windows. This approach therefore offers a principled way to diagnose, predict, and ultimately engineer emergent dynamics in neural systems and other complex networks, providing a new conceptual bridge between abstract mathematics, neuroscience, and engineering.

Disclosures: J. Li: None. S. Pardo Guerra: None. G.A. Silva: None. K. Basu: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.07/OO9

Topic: J.06. Computation, Modeling, and Simulation

Title: Fisher Information Diffusion in Deep Networks Reveals Recurrent-Feedforward Architecture with Selective Feedback

Authors: *H. QIN¹, T. O. SHARPEE²;

¹UCSD, San Diego, CA; ²CNL-T, Salk Inst., San Diego, CA

Abstract: Recurrent neural networks (RNNs), both biological and artificial, leverage complex recurrent dynamics and structured connectivity to perform sophisticated computational tasks, yet a rigorous theoretical framework connecting these properties to information retention and transmission remains elusive. In this paper, we present an analytical framework with Fisher information to quantify and optimize the encoding and propagation of input information in large-scale, structured recurrent neural networks composed of multiple interacting neuronal subpopulations. By introducing the Fisher diffusion operator and using dynamic mean-field approximations, the theory shows that achieving criticality (i.e., operating at the spectral radius equal to one, or "edge of chaos") is necessary but not sufficient for optimal information retention. Instead, the optimal network structure emerges as a nearly feedforward architecture augmented by strategically positioned and controlled feedback loops. This configuration connects classical random matrix theory results, including the Johnson-Lindenstrauss lemma and the restricted isometry property (RIP), with nonlinear dynamic stability at the edge of chaos. Overall, our framework provides foundational insights into the interplay between network connectivity, spectral stability, and information dynamics, establishing guiding principles for designing efficient and robust recurrent neural architectures.

Disclosures: H. Qin: None. T.O. Sharpee: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.08/OO10

Topic: J.06. Computation, Modeling, and Simulation

Support: NEI Grant EY032179
NSF Fellowship DGE-1752814

Title: Deep Sparse Coding

Authors: *H. VAFAI¹, D. GALOR³, J. YATES²;

¹UC Berkeley, Berkeley, CA; ²Optometry, UC Berkeley, Oakland, CA; ³Vision Sci., Univ. of California, Berkeley, Berkeley, CA

Abstract: Brains excel at out-of-distribution (OOD) generalization, where conventional machine learning models often struggle. This superior OOD capacity of biological intelligence may be enabled by the sparse, compositional representations observed throughout the cortex, particularly in visual areas. While sparse coding models provide a natural computational framework for capturing these brain-like sparse representations, they typically employ linear decoders, which limit their expressivity and adaptability.

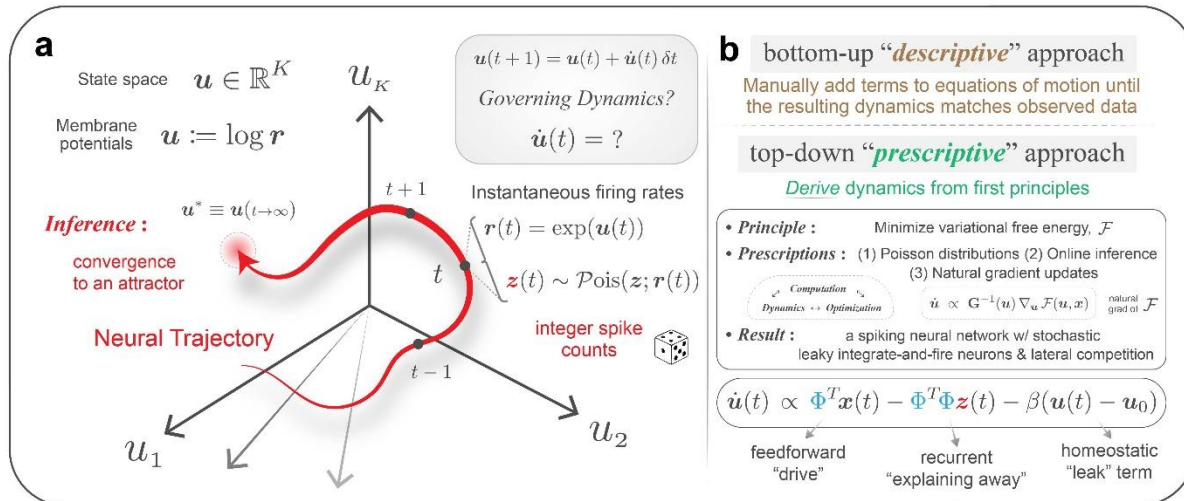
Here, we extend classical sparse coding models to incorporate deep, nonlinear decoders, including convolutional and multi-layer perceptron architectures. We derive the iterative encoding dynamics following the brain-inspired FOND framework (Vafai et al., 2025 [1]) and demonstrate that this nonlinear extension yields several key advantages.

First, the nonlinear decoder enhances model adaptivity by making the iterative encoding algorithm explicitly dependent on the current neural state. This creates context-sensitive encoding dynamics that adapt the computational pathway based on the evolving neural representation. In contrast, classical linear sparse coding uses a fixed dictionary and encoding algorithm. **Second**, we demonstrate that this nonlinear decoder extension achieves superior OOD generalization performance in both within-dataset perturbations and cross-dataset settings, outperforming classical linear sparse coding and modern deep learning models such as hybrid iterative-amortized variational autoencoders. Remarkably, the deep sparse coding model trained on MNIST digits successfully generalizes to cropped, grayscale natural images.

These results show that combining deep learning with sparse, compositional codes yields improved generalization and computational efficiency, establishing a promising direction for biologically-inspired architectures.

[1] Vafai et al., 2025: arxiv.org/abs/2410.19315

The FOND framework:



Disclosures: H. Vafaii: None. D. Galor: None. J. Yates: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.09/OO11

Topic: J.06. Computation, Modeling, and Simulation

Support: NSF FGNM06

Title: Global distortions from local rewards: Neural coding strategies in path-integrating RNNs

Authors: *F. ACOSTA¹, F. DINC³, W. REDMAN⁴, M. S. MADHAV⁵, D. KLINDT⁶, N. MIOLANE²;

²ECE, ¹Geometric Intelligence Lab, UC Santa Barbara, Santa Barbara, CA; ³Kavli Inst. for Theoretical Physics, UC Santa Barbara, Santa Barbara, CA; ⁴Dynamical Neurosci., Johns Hopkins Applied Physics Lab., Laurel, MD; ⁵Sch. of Biomed. Engin., Univ. of British Columbia, Vancouver, BC, Canada; ⁶Cold Spring Harbor Lab., Laurel Hollow, NY

Abstract: Grid cells in the mammalian brain are fundamental to spatial navigation, and therefore crucial to how animals perceive and interact with their environment. Traditionally, grid cells are thought support path integration through highly symmetric hexagonal lattice firing patterns. However, recent findings show that their firing patterns become distorted in the presence of significant spatial landmarks such as rewarded locations. This introduces a novel perspective of dynamic, subjective, and action-relevant interactions between spatial representations and environmental cues. Here, we propose a practical and theoretical framework to quantify and explain these interactions. To this end, we train path-integrating recurrent neural networks (piRNNs) on a spatial navigation task, whose goal is to predict the agent’s position with a special

focus on rewarded locations. Grid-like neurons naturally emerge from the training of piRNNs, which allows us to investigate how the two aspects of the task, space and reward, are integrated in their firing patterns. We find that geometry, but not topology, of the grid cell population code becomes distorted. Surprisingly, these distortions are global in the firing patterns of the grid cells despite local changes in the reward. Our results indicate that after training with location-specific reward information, the preserved representational topology supports successful path integration, whereas the emergent heterogeneity in individual responses due to global distortions may encode dynamically changing environmental cues. By bridging the gap between computational models and the biological reality of spatial navigation under reward information, we offer new insights into how neural systems prioritize environmental landmarks in their spatial navigation code.

Disclosures: F. Acosta: None. F. Dinc: None. W. Redman: None. M.S. Madhav: None. D. Klindt: None. N. Miolane: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.10/OO12

Topic: J.06. Computation, Modeling, and Simulation

Support: NSF DBI 2015317

Title: Designing the bump: unified rules for the design of neural attractor models across species and functionality

Authors: *W. R. P. NOURSE¹, R. D. QUINN²;

¹Mechanical and Aerospace Engin., ²Mechanical Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: While neural computation occurs in high dimensional spaces, the resulting activity can often be understood when projected into a lower dimensional subspace or manifold. This can be seen in multiple instances of real neural systems, including those for sensory processing (insect central complex, mammalian head direction cells), navigation (grid cells), and motor control (motor cortex, spinal cord). In all of these systems, there is a specified region (or “bump”) of active neurons, which propagates through the network either autonomously or in the presence of external stimuli. Multiple computational models have been proposed which replicate all or some of this behavior, including (but not limited to) stable-heteroclinic channels (SHCs), ring attractors, continuous attractor networks (CANNs), low-rank recurrent neural networks, and balanced recurrent neural networks. Knowing that there are multiple topologies and mechanisms which generate variants of the same population dynamics, how can we best design a network which has the manifold dynamics we desire? In this work, we explore how one can design an attractor network for a desired functionality, analyzing the similarities and differences between

existing architectures. We also present some considerations when implementing these systems on neuromorphic hardware.

Disclosures: W.R.P. Nourse: None. R.D. Quinn: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.11/OO13

Topic: J.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI Grant Number JP24K15104
JSPS KAKENHI Grant Number JP21H02597
Japan Agency for Medical Research and Development (AMED) AMED-CREST JP25gm1510005s0205

Title: Trade-off between memory capacity and trajectory amplification in transient neural dynamics for sensory discrimination

Authors: *A. TOMOTO, J.-N. TERAMAE;
Kyoto Univ., Kyoto, Japan

Abstract: Conventional models of sensory coding and memory retrieval have primarily focused on steady-state neural activities, represented as stable fixed points or attractors in the high-dimensional space of neural activity. However, with the rapid development of experimental techniques, recent studies have revealed that the trajectories of transient neural activity, occurring before convergence to steady states, are more informative for discriminating sensory stimuli than the steady-state activities themselves. For instance, projection neurons (PNs) in the locust antennal lobe have been shown to exhibit odor-specific dynamic responses, with optimal odor separation occurring during the transient periods of population activity rather than at the steady states, where activity is assumed to converge to a fixed point (Mazor & Laurent, 2005). While a model to generate transient neural trajectories has been proposed, its simplicity prevents it from fully capturing important experimental findings, such as the existence of multiple attractors and the stimulus dependence of trajectories. To address this limitation, we developed a theoretical framework for a recurrent network model that incorporates multiple stimulus-dependent amplified trajectories. In this model, dynamical memories are embedded in the network through connections with a hetero-associative memory structure. Input stimuli to the memory are more clearly distinguished during the transient dynamics than at the fixed points of the neural networks. By developing a mathematical theory of transient memory dynamics based on random matrix theory, we derived the stability conditions for a network exhibiting amplification along transient trajectories. Significantly, we reveal a fundamental trade-off between the memory capacity of the recurrent network with dynamical memory and the magnitude of transient amplification of the embedded trajectories. This finding implies that

dynamic sensory representation in the brain must achieve a balance between the number of possible trajectories and their separability. Considering the accumulating evidence highlighting the significance of dynamic information representation across various brain regions, this work, by clarifying fundamental principles of dynamic information coding, may serve as a foundation for future theoretical and experimental investigations in neuroscience.

Disclosures: **A. Tomoto:** None. **J. Teramae:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Japan Society for the Promotion of Science, Japan Agency for Medical Research and Development.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.12/OO14

Topic: J.06. Computation, Modeling, and Simulation

Title: Subcritical operating regimes and circuit motif organization confer robustness to perturbation

Authors: ***G. TOLOSSA**¹, K. BHASKARAN-NAIR², A. ARKHIPOV³, K. B. HENGGEN⁴;
¹Washington Univ. in St. Louis Neurosci. PhD Program, St. Louis, MO; ²Dept. of Biol., Washington Univ. in St. Louis, St. Louis, MO; ³Allen Inst., Seattle, WA; ⁴Biol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: The critical brain hypothesis posits that neural networks operate at the edge of stability and chaos, near critical dynamics where information encoding, transmission, and storage are optimized. However, operating close to criticality carries the risk of transitioning into chaotic states, which can be pathological. Therefore, the brain must maintain proximity to critical dynamics while avoiding catastrophic transitions to chaos. The mechanisms enabling this balance remain unclear. In this study, we hypothesize that cortical architecture plays a key role in maintaining this balance. To test this, we systematically construct and perturb models of varying complexity, ranging from biophysically detailed simulations to simplified cortical branching models. We examined how specific circuit motifs and canonical cortical microarchitectures contribute to network dynamics that are both stable and sensitive to perturbations. Our results show that slightly subcritical networks provide a broader safe operating range against perturbations. Furthermore, diverse inhibitory cell subtypes and their associated circuit motifs enable richer responses to perturbations.

Disclosures: **G. Tolossa:** None. **K. Bhaskaran-Nair:** None. **A. Arkhipov:** None. **K.B. Hengen:** None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.13/OO15

Topic: J.06. Computation, Modeling, and Simulation

Support: DOE ASC Program

Title: Feedback control is the core function of neural systems

Authors: *F. ROTHGANGER;

Cognitive & Emerging Computing, Sandia Natl. Labs., Albuquerque, NM

Abstract: The brain is a complex system with many interacting components. The task of mathematically modeling this system can seem overwhelming, certainly beyond the ability of any single human. However, there are patterns that recur in many existing models across a wide range of scales. They tend to have dynamics, that is, equations that express how quantities evolve through time in response to other quantities. They also tend to have feedback loops that keep the system near some “ideal” state.

The pattern of dynamical systems implementing feedback control is general enough to describe such diverse phenomena as spike transmission (the Hodgkin-Huxley model), regulation of synaptic density, axon guidance, learning, and decision-making (ethology). We present select examples, then show how to apply this idea in your own research. The long-term value of using a common framework is to synthesize a general theory of neural function.

Disclosures: F. Rothganger: A. Employment/Salary (full or part-time): Sandia National Laboratories.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.14/OO16

Topic: J.06. Computation, Modeling, and Simulation

Title: Indoctrinating students is harder than you think: highly constraining RNNs is no guarantee of their quality as surrogates for the brain

Authors: *P. JIANG¹, H. GIAFFAR¹, Z. JIN¹, Y. YUAN², A. CHARLES⁴, M. AOI^{3,5,1};

¹Halicioğlu Data Sci. Inst. (HDSI), ²Dept. of Neurosciences, ³Neurobio., UC San Diego, La Jolla, CA; ⁴Johns Hopkins Univ. - Homewood Campus, Lutherville-Timonium, MD; ⁵Hdsi, Univ. of California San Diego, La jolla, CA

Abstract: Recurrent neural networks (RNNs) have become a cornerstone of modeling neural time-series data, and have been successfully trained to either perform behavioral task(s) or to recapitulate neural data. The goal of this exercise is often to have the RNN serve as a surrogate for the brain itself, which can then be reverse engineered and arbitrarily experimentally manipulated to discover the computational mechanisms employed by the brain. However, the degeneracy in the RNN input / output mapping leaves open the possibility that the mechanistic interpretations of trained RNNs may not accurately reflect brain function. This can happen when the details of the learned computation differ from the data-generating system. Here, we use a multitask trained RNN as a virtual "teacher" network and treat it as though it were a brain, and train "students" on both the outputs and a portion of the activity of the teachers. To simplify this setting to be amenable to systematic analysis we 1) make all students have the same architecture and network size as the teacher, 2) devised a multitask simulation setting that we believe is minimal in its design. We compared high-performing students (i.e. low MSE) with teachers generated using different training schedules (i.e., interleaved vs. continual learning) on features of neural activity such as selectivity, dynamics, and connectivity. When students were successfully indistinguishable from teachers we called this "indoctrination". We find that strong indoctrination is not guaranteed even if 100% of teacher neurons are recorded and that higher proportions of recorded neurons is no guarantee of greater success. We hope our results will guide the design of future experiments, both real and simulated.

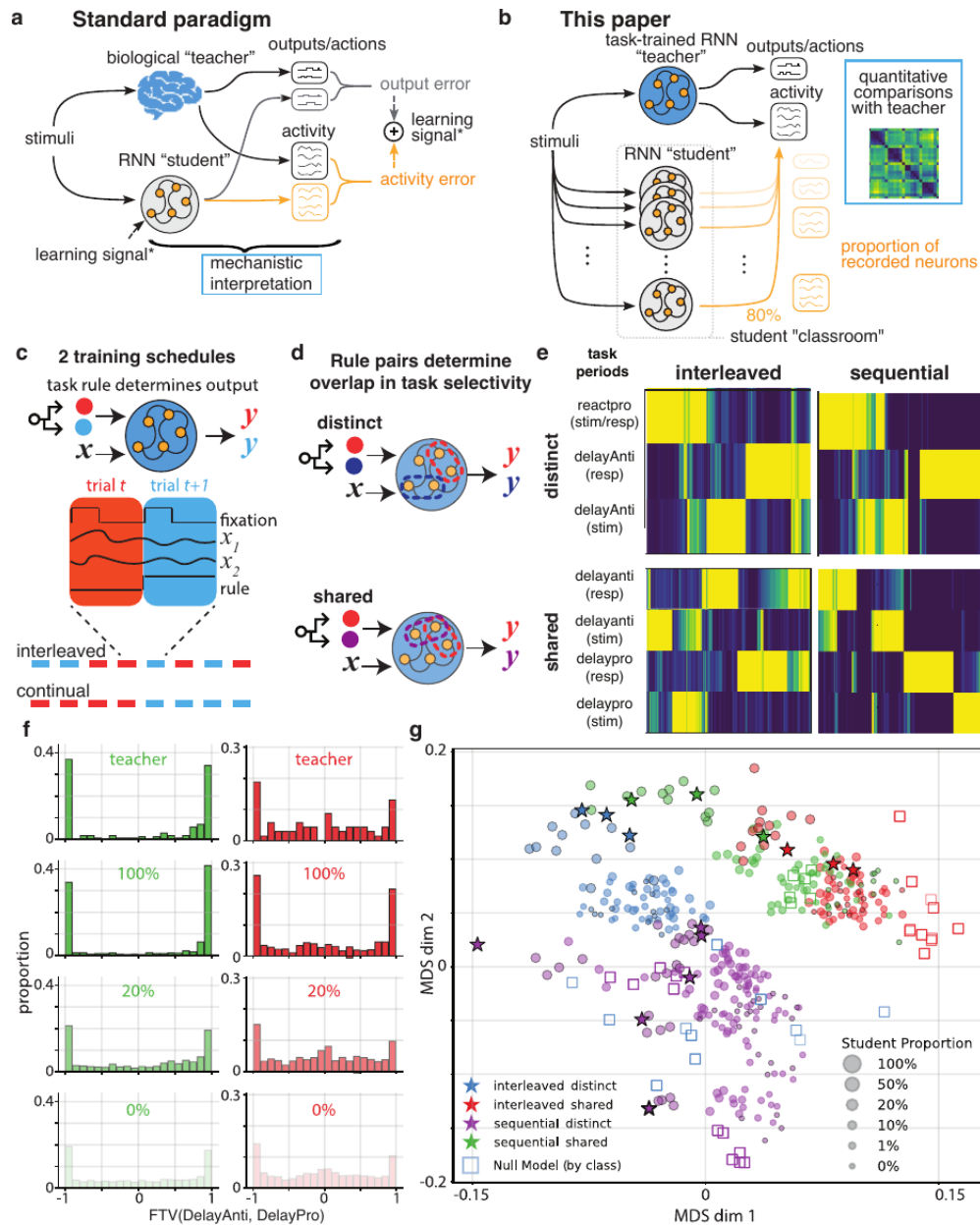


Figure 1. (a) Standard paradigm using a data-drive RNN to investigate the brain. **(b)** Our paradigm: use a task-trained RNN as a virtual brain ("teacher"), and train a bunch of RNNs as "students" to reproduce the input-output relationship as well as a proportion of activity of "teacher". **(c, d)** Our ways to train the networks. **(c)** Train the RNN in an interleaved or continual-learning manner. **(d)** Train each RNN with two tasks from either a 'distinct motif', where the neurons are supposed to develop non-overlapping clusters for each task, or a 'shared motif', where some neurons participate in both tasks. **(e)** Networks' normalized activity variance of four sample teachers. Overlapping in columns indicates a shared group of neurons is activated in both task periods. **(f, g)** One sample analysis result: Fractional task variance (FTV). **(f)** Sample FTV from two teachers and selected students. **(g)** MDS plot for Jensen-Shannon distance among all FTV distributions. Even students trained on 100% teacher's activity don't exhibit exactly the same FTV distribution as their teachers.

Disclosures: P. Jiang: None. H. Giffar: None. Z. Jin: None. Y. Yuan: None. A. Charles: None. M. Aoi: None.

Poster

PSTR050: Deep or Recurrent Networks: Theory and Modeling I

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR050.15/OO17

Topic: J.06. Computation, Modeling, and Simulation

Title: A Collective Perspective of Perceptual Decision-Making Tasks with Recurrent Neural Networks Ensemble

Authors: *Z. JIN¹, M. AOF²;

²Neurobio. & Data Sci., ¹UCSD, San Diego, CA

Abstract: Recurrent Neural Networks (RNNs) have emerged as powerful tools for modelling complex temporal dynamics of cognitive processes in neuroscience, particularly in perceptual decision-making (PDM) tasks. In these PDM tasks, biological agents sample from a series of stimuli to reach a final decision. Prior studies that trained RNNs to analyse PDM typically trained a single RNN that either performs the tasks well or best replicates observed data. However, this approach relies on an implicit assumption that it fully captures the underlying mechanisms, and thus risks overlooking uncertainty in the conclusions drawn from the trained network. In this work, we propose an ensemble approach to evaluate complex systems from a collective perspective. We simulated a PDM task with varying evidence-to-noise. Then, we implemented an ideal drift diffusion model (DDM) agent that accumulated noisy stimuli and decided once the evidence level reached a boundary. Next, we trained an RNN on the outputs of the ideal agent served as a virtual "brain", which we wish to understand. To this end, we finally trained an ensemble of RNNs spanning multiple cell types to learn the outputs of the conditioning RNN. We found that the individual data-driven RNNs that matched the architecture of the conditioning RNN achieved the lowest mean squared error (MSE) on the full dataset. Additionally, larger networks generally outperformed smaller ones. Moreover, complex cell types substantially outperformed simpler architectures. This suggests an architectural affinity between the networks and their modelled biological counterparts. We also studied the collective performance of the ensemble. We defined a selection criterion based on prediction MSE across the full dataset. The preliminary results suggest that ensemble predictions can yield better performance than the best single network. Moreover, we also found that by choosing an appropriate ensemble the uncertainty of the prediction was minimised. These findings suggest that by employing ensemble techniques we could obtain both better performance and better control over the certainty of the prediction of a biological brain, offering a more holistic understanding of the modelled behaviour. Future directions include improving task simulation and ensemble quality. We plan to adopt tasks beyond the drift diffusion, as well as to introduce biological constraints to further mimic the brain. We also plan to weight individual networks by performance and employ evolutionary algorithms to identify optimal configurations., and aim to analyse internal network properties beyond outputs, including eigenvalue spectra and dynamical topologies.

Disclosures: Z. Jin: None. M. Aoi: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.01/OO18

Topic: J.07. Data Analysis and Statistics

Title: A meta-analysis on the effectiveness of transcranial direct current stimulation (tDCS) on the processing of implicit associations (IATs) in men and women

Authors: *A. M. CROOM;

Cognitive Sci., Case Western Reserve Univ., Cleveland, OH

Abstract: Results from experimental research remain conflicted about the effectiveness of using transcranial direct current stimulation (tDCS) to reduce implicit bias in participants. To determine the general effectiveness of tDCS on implicit bias across studies, a meta-analysis of all relevant studies involving tDCS and implicit association tests (IATs) was therefore conducted. Using a random-effects model, this meta-analysis found no significant effect for tDCS versus sham on implicit bias scores among all participants ($k = 39$, $SMD = -0.063$, $p = 0.311$). Further subgroup analyses also found no significant effect for tDCS versus sham on implicit bias scores in males ($k = 14$, $SMD = -0.236$, $p = 0.107$) or females ($k = 14$, $SMD = 0.054$, $p = 0.470$). Results also showed no significant effect for tDCS versus sham on response times among all participants ($k = 78$, $SMD = -0.043$, $p = 0.472$). However, further subgroup analyses revealed a small yet significant effect for tDCS versus sham on increasing response times in males ($k = 28$, $SMD = 0.252$, $p = 0.012$) and a very small yet significant effect for tDCS versus sham on decreasing response times in females ($k = 28$, $SMD = -0.140$, $p = 0.026$). A between-group heterogeneity test further indicated that sex significantly moderated the effect of tDCS on response times across groups ($Q\text{-between} = 14.828$, $df = 2$, $p < 0.001$). Potential factors for sex differences in the response times of men and women include differences in anatomy (skull thickness), hormone regulation (testosterone and estrogen), neurotransmitter dynamics (GABA modulation), and neural network organization (baseline connectivity and flexibility). Finally, several publication bias assessments, including Fail-Safe N and Trim and Fill Number of Studies, indicate no publication bias for studies on men but some publication bias for studies on women, suggesting that sex differences in the results may also reflect some publication bias in the extant literature.

Disclosures: A.M. Croom: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.02/Web Only

Topic: J.07. Data Analysis and Statistics

Title: Cross-tissue analysis of sex-associated gene expression reveals blood signatures linked to neurological disease risk

Authors: *L. YUAN¹, X. ZHOU²;

¹Queen Mary Univ. of London, London, United Kingdom; ²Genet. & Genome Biol., The Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Sex differences in brain function and neurological disease susceptibility are well established, but underlying molecular mechanisms remain unclear. Immune-related pathway alterations are observed in central and peripheral tissues, yet their link to sex differences is understudied. Gene expression data from GTEx included 670 blood and 2,181 brain samples across 13 regions. Sex-associated genes were identified via linear regression with sex as the primary predictor, adjusting for age, RNA integrity, and platform. Genes with FDR < 0.05 were considered significant. Pearson correlation assessed blood-brain concordance, and GO enrichment was performed using g:Profiler. Meta-analysis of brain data identified 866 sex-associated genes (431 female-enriched, 435 male-enriched). Female-enriched genes were associated with X-linked inheritance, blood vessel development, and nervous system development, while male-enriched genes were linked to Y-linked inheritance, cytokine signaling, and immune receptor activity. In blood, 427 sex-associated genes were detected (379 female-enriched, 48 male-enriched). Female-enriched genes were related to immune receptor activity and chromatin binding, whereas male-enriched genes were involved in immune responses and leukocyte activation. Blood-brain expression correlation was significant ($R = 0.499$, $p < 0.01$). Cross-tissue clustering revealed three groups of genes with altered expression in blood or brain tissues: Group 1 ($n = 52$), brain-specific genes enriched for neuronal functions; Group 2 ($n = 298$), blood-specific genes involved in immune responses; and Group 3 ($n = 375$), shared genes related to immune regulation and metabolic processes. This study reveals both shared and tissue-specific patterns of sex-biased gene expression in the human brain and peripheral blood. The identification of a shared transcriptomic signature supports the potential of using blood-based biomarkers to reflect sex-specific molecular states in the central nervous system, offering insights into sex-differentiated risk for neurological diseases.

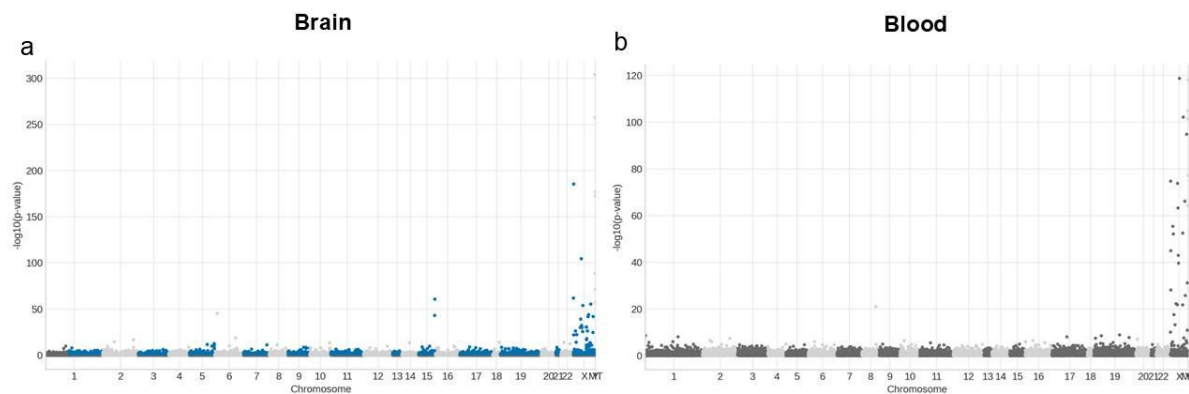


Figure 1. Manhattan plots showing genes associated with sex in transcriptome analyses of brain and blood tissues.

Manhattan plots display p-values for sex-associated gene expression in **(a)** brain and **(b)** blood tissues. In **(a)**, data are derived from a meta-analysis of RNA-seq profiles across 13 brain regions from the GTEx. In **(b)**, data are derived from RNA-seq profiles of blood samples from GTEx.

Disclosures: L. Yuan: None. X. Zhou: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.03/PP1

Topic: J.07. Data Analysis and Statistics

Support: SECIHTI
GYV-C received the scholarship No. 747917 from SECIHTI for postgraduate studies.

Title: Inferential statistics resources in psychology: A perspective study

Authors: *G. VARELA CASTILLO¹, D. HERNANDEZ-BALTAZAR², B. BERNAL-MORALES³;

¹Facultad de Psicología, Univ. Veracruzana, Xalapa, Mexico; ²CONACYT-Instituto de Neuroetología., Mexico; ; ³Univ. Veracruzana, Inst. de Neuroetología, Xalapa.

Abstract: The most common errors in statistical analysis are related to a poor understanding of statistical inference and parametric tests. The main goal of this contribution is comparing the criteria used in existing statistical models in psychological sciences. For this, a systematic review of publications focused on the teaching and use of ad hoc statistical models for the social sciences was conducted. In the present contribution, we discuss the need to establish a robust

"mutuality" between statistics and psychology from their historical context and practical use, which will help us ensure the integrity and validity of its assumptions.

Disclosures: G. Varela Castillo: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.04/PP2

Topic: J.07. Data Analysis and Statistics

Title: Cardiovascular and autonomic responses to modulated breathing with controlled minute ventilation

Authors: *H. CHOI¹, C. KIM³, D. JANG², P. H. MIN⁴, J. LEE⁵;

¹Hanyang Univ., Seongdong-gu, Seoul, Korea, Republic of; ²Biomed. Engin., Hanyang Univ., Seoul-City, Korea, Republic of; ³Electronic engineering, Dept. of electronic engineering, Hanyang Univ., Seoul, Korea, Republic of; ⁴Neural Engin., Mayo Clin., Rochester, MN;

⁵Radiology, Hanyang university, Seoul, Korea, Republic of

Abstract: The glymphatic system, a brain-wide fluid clearance pathway, has recently gained attention for its role in removing neurotoxic waste products. This system becomes active during sleep, when cerebrospinal fluid (CSF) flows into the interstitial space and facilitates metabolic waste clearance. While various factors are known to influence glymphatic activity, we propose respiration as a novel driving force that may accelerate CSF flow and enhance glymphatic function. During inhalation, thoracic expansion generates negative pressure, increasing venous return and thereby boosting cardiac output (CO), which in turn may promote CSF movement within the brain. In this study, we investigated how changes in breathing rate and minute ventilation (MV) affect cardiovascular and autonomic responses—including heart rate (HR), stroke volume (SV), CO, and heart rate variability (HRV)—in healthy adults. Nineteen participants completed a breathing protocol consisting of a 5-minute rest phase, a 5-minute modulated breathing phase, and a 5-minute post-rest phase. Four breathing conditions were tested: (1) Rest BR (MV = 100%), (2) Rest BR (MV = 180%), (3) 6 Breaths/min (MV = 100%), and (4) 6 Breaths/min (MV = 180%), (BR = breathing rate). Our results demonstrated that increasing MV by 80%, regardless of breathing rate, significantly elevated HR and CO ($p < 0.01$), while SV remained stable at the group level. Breathing rate changes without MV increase showed no significant cardiovascular effects. These findings indicate that minute ventilation is a key determinant of CO modulation, rather than breathing rate alone. Additionally, a transient co-activation of HR and HRV was observed during the first 1-2 minutes of slow breathing (6 Breaths/min), followed by a return to baseline. This response—only detectable through minute-by-minute analysis—challenges the conventional view of HR and HRV as inversely related and highlights the value of high temporal resolution in autonomic research. In conclusion, respiratory-driven increases in MV may enhance cardiac output, potentially facilitating CSF

circulation and glymphatic clearance. These findings support the physiological basis for using breathing modulation in brain waste clearance and autonomic interventions.

Disclosures: H. Choi: None. C. Kim: None. D. Jang: None. P.H. Min: None. J. Lee: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.05/PP3

Topic: J.07. Data Analysis and Statistics

Support: Postdoctoral fellowship from DGAPA-UNAM awarded to the presenting author.
Postdoctoral fellowship from SECIHTI awarded to the presenting author.
Ph.D. fellowship from SECIHTI 823584 awarded to the second author.
DGAPA-PAPIIT-UNAM IN208622.
Leopoldo González Santos, Technical Assistance.
Omar González Hernández, Technical Assistance.

Title: The Maximum Spanning Tree reveals differences between the topology of functional networks in at-term and preterm infants

Authors: *J. DIAZ-PATINO¹, N. LÓPEZ GUERRERO², I. ARELIO¹, S. ALCAUTER²;
¹Inst. de Matemáticas, UNAM, Queretaro, Mexico; ²Neurobiología Conductual y Cognitiva, Inst. De Neurobiología. Univ. Nacional Autónoma de México, Querétaro, Mexico

Abstract: Despite rapid brain maturation after birth, the global functional connectivity properties of preterm infants differ¹. Here, we estimated the maximum spanning tree (MST) of the functional brain connectome to characterize topological differences between at-term and preterm neonates. We used 392 datasets from the developing Human Connectome Project² acquired at a term-equivalent age with no radiological signs of white matter lesions, and the atlas AAL adapted to neonatal brains, which provides a parcellation into seven anatomical subregions. The data are divided into groups according to weeks of gestation: 61 preterm and 331 at-term. We computed the MST of each functional brain connectome and its respective weighted MST (wMST). We then calculated the contribution of each anatomical subregion by adding the link weights within that subregion and dividing by the wMST. Finally, we compared these proportions between the at-term and preterm groups. We found significant differences between groups in the wMST in the whole brain connectome ($t = 6.8$, $df = 73.7$, $p = 1.5 \times 10^{-9}$) and the proportional contribution of specific subregions to the wMST between at-term and preterm neonates. After adjusting p-values using false discovery rate, we observed differences in the Limbic, Parietal-Temporal, Fronto-Parietal, Limbic-Subcortical, and Subcortical subregions (Fig. 1). These findings suggest that preterm birth is associated with increased connectivity in subcortical and limbic systems, as well as decreased connectivity within higher-order associative

subregions. The MST provides insights into the reorganization of functional networks during early developmental stages, which may influence future cognitive and socioemotional outcomes³.

1. López-Guerrero & Alcauter (2025) --<https://doi.org/10.1002/hbm.70126> 2. Hughes et al. (2017)-- <https://doi.org/10.1002/mrm.26462> 3. Eyre et al. (2021)-- <https://doi.org/10.1093/brain/awab118>

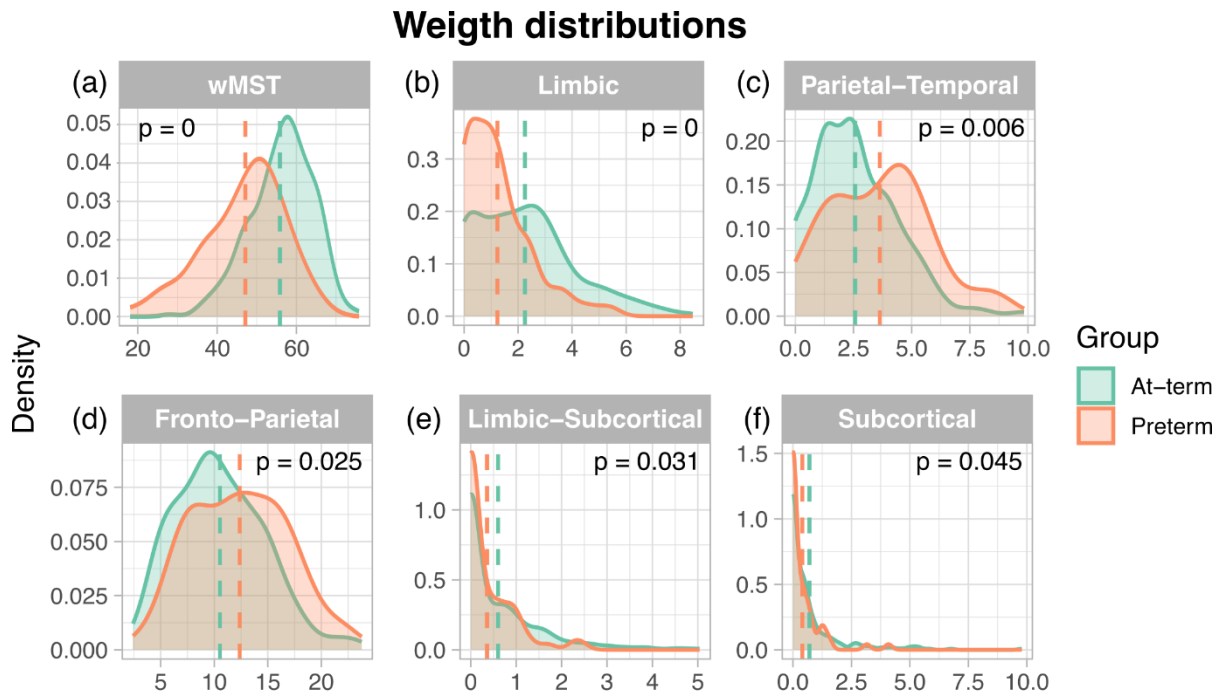


Figure 1. Panel (a) shows the distributions of the wMST between groups. Panels (b-f) show the distributions of the proportions of the wMST for each subregion, including only those with significant differences.

Disclosures: J. Diaz-Patino: None. N. López Guerrero: None. I. Arelio: None. S. Alcauter: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.06/PP4

Topic: J.07. Data Analysis and Statistics

Title: Exploring SVZ Proximity in Occipital Glioblastoma: A Case-Inspired Transcriptomic Hypothesis on Tumor Recurrence

Authors: M. RAMÍREZ¹, I. SIMPSON¹, S. BARRENO ROCHA¹, G. GARCIA ORDOÑEZ³, Á. REYES-QUINTERO⁴, K. AHMAD², *L. E. ÁLVAREZ-PALAZUELOS^{5,1};

¹Neurosci. and Res., Univ. Autónoma de Guadalajara, Guadalajara, Mexico; ²Neurosci. and Res., Univ. Autónoma de Guadalajara, Zapopan, Mexico; ³Doctorado en Ciencias Biomédicas, ⁴Doctorado en Genética Médica, Univ. de Guadalajara, Guadalajara, Mexico; ⁵Neurosci., Univ. De Guadalajara, Guadalajara, Mexico

Abstract: Background: Glioblastoma (GBM) is the most aggressive and prevalent primary malignant brain tumor in adults; most lesions arise in the frontal and temporal lobes, whereas occipital tumors comprise <5% of cases. Contact with the subventricular zone (SVZ) has been linked to enhanced migration, distant recurrence and worse prognoses. We present a case of a right-occipital GBM with atypical septal-callosal recurrence and use this clinical finding as the foundation to propose and conduct a pilot bioinformatics exploration of posterior SVZ-contacting GBMs. **Objective:** To characterize the clinicopathological and molecular features of a posterior GBM with septal recurrence and to draft a hypothesis-generating bioinformatics framework capable of identifying common gene expression signatures associated with SVZ involvement in posterior gliomas. **Methods:** A 60-year-old man with a right occipital IDH-wildtype GBM underwent tumor resection followed by the full Stupp protocol. Recurrence in the septum pellucidum and corpus callosum prompted histopathological re-evaluation, which revealed up-regulation of invasion-associated markers. Guided by these findings, we mined TCGA and CGGA transcriptomes to identify gene expression patterns in posterior GBMs with and without SVZ contact; the REMBRANDT cohort (GSE108474) provided external validation. Differential-expression analysis was followed by functional-enrichment and protein-protein interaction mapping, prioritizing genes related to stemness, and migratory capacity. **Results:** The primary lesion extended toward the lateral ventricular atrium, suggesting SVZ involvement. Recurrent lesion analysis demonstrated increased expression of *CD44*, *SOX2*, and *CXCR4*. Bioinformatics analysis confirmed enrichment of these genes in SVZ-contacting gliomas across public datasets. Functional enrichment identified ECM remodeling, chemokine signaling, and neurodevelopmental pathways as commonly activated processes. **Conclusion:** This case-inspired exploratory analysis supports the hypothesis that SVZ proximity may drive a distinct molecular trajectory in occipital glioblastoma. The proposed bioinformatic framework developed from this case provides a reproducible strategy to further explore SVZ-associated dissemination in posterior gliomas. Spatial-transcriptomic and single-cell studies are warranted to validate these observations. **Keywords:** Glioblastoma, occipital lobe, subventricular zone, CXCR4, CD44, tumor migration, recurrence, bioinformatics

Disclosures: M. Ramírez: None. **I. Simpson:** None. **S. Barreno Rocha:** None. **G. Garcia Ordoñez:** None. **Á. Reyes-Quintero:** None. **K. Ahmad:** None. **L.E. Álvarez-Palazuelos:** None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.07/PP5

Topic: J.07. Data Analysis and Statistics

Support: NRF Grant RS-2025-00522357

Title: Effects of Visual Cues on Musical Melody Imagery for EEG-based Music Brain-computer Interfaces

Authors: *C. YOON¹, S.-P. KIM²;

¹Ulsan Natl. Inst. of Sci. Technol., Ulsan, Korea, Republic of; ²Biomed. Engin., Ulsan Natl. Inst. of Sci. and Technol., Ulsan, Korea, Republic of

Abstract: Decoding imagined musical pitch from electroencephalography (EEG) remains a challenge in the development of music brain-computer interfaces (BCIs), primarily due to ambiguous and inconsistent EEG responses to music imagery. Based on findings in motor imagery BCIs showing that different sensory modalities such as visual or kinesthetic cues can foster motor imagery, this study investigates whether visual cues facilitate music imagery and the reliability of EEG responses. We compared EEG responses across several types of visual cues during both the perception and imagination of musical pitch sequences. Ten musically trained participants listened to five-tone melodies generated from seven piano tones in the 4th octave (C4-B4; Do, Re, Mi, Fa So, La, and Ti), followed by the imagination of humming the same melodies. Each melody was structured using harmonic rules and Hanon-inspired ascending or descending pitch patterns. Each trial consisted of two tasks: (1) a perception task, where participants heard a melody while one of the four visual cues was presented—a keyboard image, letter name, musical notation, or a static note symbol. All cues except the static note symbol were animated to be semantically congruent with the melody. (2) A subsequent imagery task, where participants imagined the same melody while viewing only the static symbol, regardless of the preceding visual cue. This design allowed us to investigate which types of visual cues best support musical imagery while avoiding confounds during the imagery task itself. During the perception task, event-related potentials (ERPs) were modulated by pitch height, with keyboard inducing more distinct ERP responses than others. Notably, even in the imagery task—where participants performed imagery with only the static symbol—ERP waveforms varied with pitch height. Interestingly, when the keyboard cue was presented during perception, the subsequent imagery task evoked ERP waveforms with reversed polarity compared to those during the perception task. This result aligns with prior findings that perception and imagery can evoke opposite neural dynamics, and further suggests that keyboard cue may amplify such contrasts. Post-experiment survey feedback also supported this implication, as participants reported that melodies paired with the keyboard cue were easier to imagine, possibly contributing to stronger internal pitch representation. However, the keyboard cue can induce lateral eye movements, emphasizing the need for artifact removal and careful visual cue design. Our results may provide insights for the utilization of visual cues in music BCIs to improve the decoding of imagined pitch.

Disclosures: C. Yoon: None. S. Kim: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.08/PP6

Topic: J.07. Data Analysis and Statistics

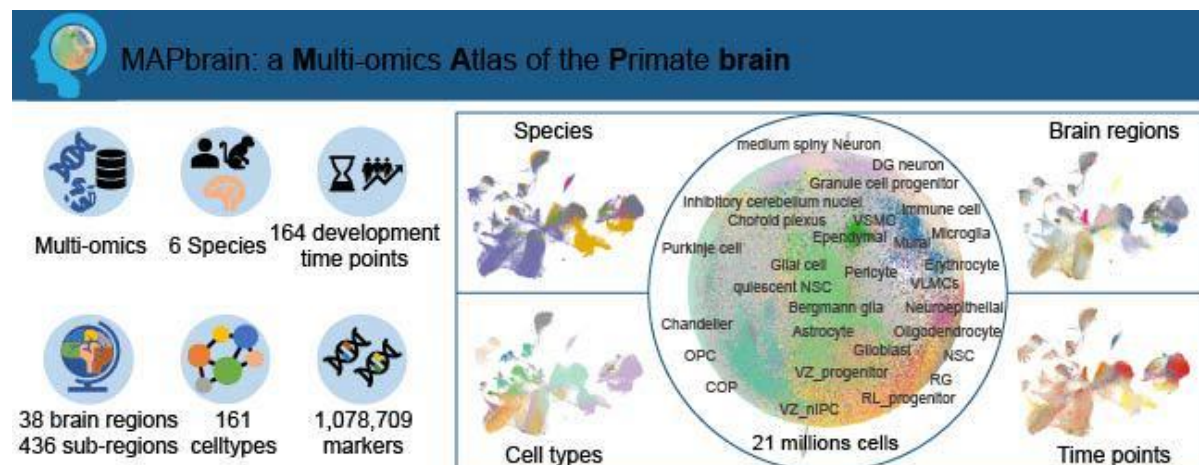
Support: 2022ZD0207700
2022YEF0203200
2021ZD0200102
2022ZD0211900
2021ZD0202403
NSFC 32192411
NSFC 32122037

Title: Mapbrain:a multi-omics atlas of the primate brain

Authors: *L. ZHUO¹, M. WANG², X. WANG³;

¹Inst. of Biophysics, Chinese Acad. of Sci., Beijing, China; ²CAS, Beijing, China; ³Inst. of Biophysics, Chinese Acad. of Scienc, Beijing, China

Abstract: The brain serves as the command center of the nervous system, and its development is a complex, lifelong journey driven by genetic instructions. Gaining insight into how genes shape brain development is essential for understanding the emergence of cognitive functions and the roots of neurological diseases. Thanks to recent advances in multi-omics technologies, researchers can now investigate these questions with unprecedented depth. However, effectively integrating and analyzing vast multi-omics datasets remains a major challenge. To address this, we present **MAPbrain** (<http://bigdata.ibp.ac.cn/mapBRAIN/>), a comprehensive multi-omics atlas of the primate brain. This resource compiles and harmonizes both our lab's published data and publicly available datasets, covering 21 million brain cells from 38 major regions and 436 subregions across both embryonic and adult stages, spanning 164 time points in humans and non-human primates. MAPbrain provides a powerful, user-friendly platform featuring transcriptomic, epigenomic, and spatial transcriptomic data. It enables in-depth investigations into brain development by supporting cell type- and time point-specific marker discovery, comparative gene expression analysis between brain regions and species, integrated analyses across molecular layers, and cross-species developmental exploration. The platform also includes an online module allowing users to upload and analyze their own data within the MAPbrain ecosystem.



Disclosures: L. zhao: None. M. Wang: None. X. Wang: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.09/PP7

Topic: J.07. Data Analysis and Statistics

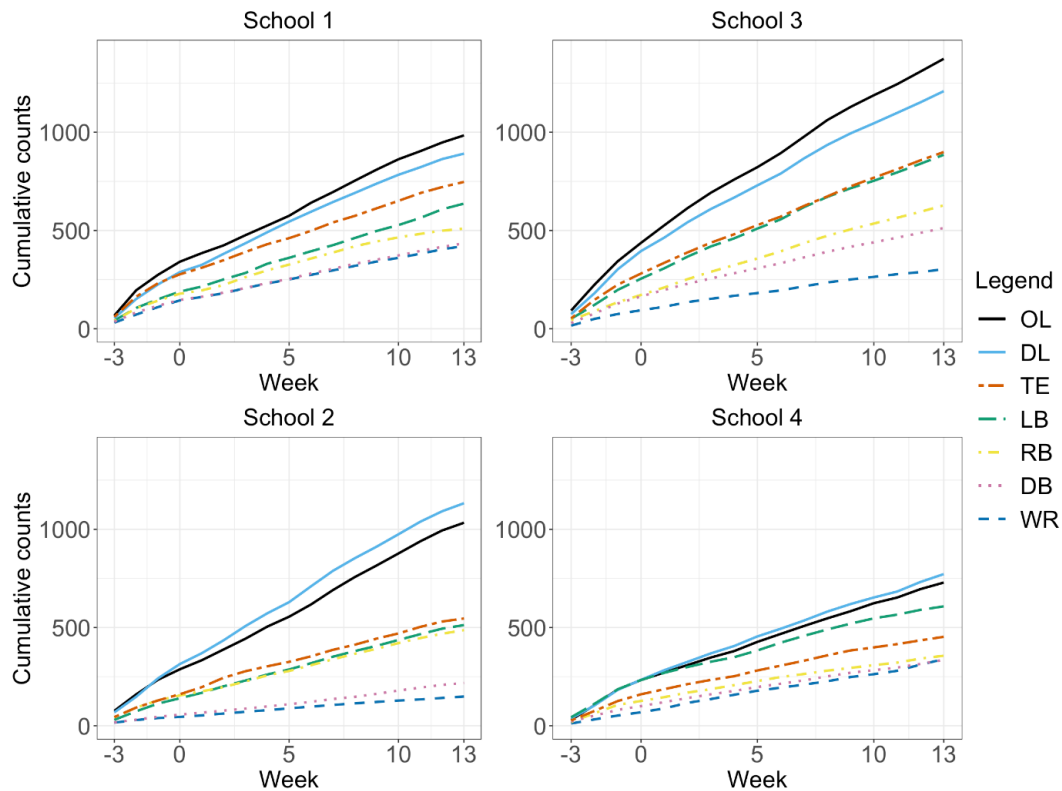
Support: NIH Grant R01NS112303

Title: Novel way of modeling associations of head impact exposure and neuropsychological outcomes among college football players

Authors: *J. HAREZLAK¹, W. WANG², L. XIAO², A. SHAH³, B. D. STEMPER⁴;
¹Indiana Univ. Sch. of Publ. Health-Bloomington, Bloomington, IN; ²North Carolina State Univ., Raleigh, NC; ³Dept. of Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI; ⁴Biomed. Engin., Marquette Univ. & Med. Col. of Wisconsin, Milwaukee, WI

Abstract: College football players often sustain impacts that might lead to concussion. Helmet-attached accelerometers track instantaneous head acceleration and are capable of detecting impacts. We use the information from longitudinally collected Head Acceleration Events (HAEs) from college football players playing at different positions and from several schools originally gathered in the CARE (Concussion Assessment Research and Education) Consortium ARC (Advanced Research Core) head impact measurements (HIM) study. We model the number of HAEs as count data and use functional data methods to quantify the varying patterns of HAEs in a season and evaluate how they might differ across positions and from school to school (See Figure 1). In particular, we decompose a matrix of functions via the Tucker decomposition of tensors, which leads to an interpretable and stable model estimation of school and position-specific mean patterns of HAEs. For the proposed model, we develop an efficient model estimation algorithm that combines expectation-maximization (EM) and nonparametric function estimation via penalized splines. In addition, we associate the extracted features of the HAEs with a number of neuropsychological outcomes and time-to-return-to-play.

Figure 1 caption: The number of HAEs per college (4 schools) and position (7 positions); OL = offensive lineman, DL = defensive lineman, TE = tight end, LB = linebacker, RB = running back, DB = defensive back, and WR = wide receiver. The x-axis shows the week during the Fall season (negative numbers show pre-season weeks), y-axis shows the cumulative number of HAEs per position and school.



Disclosures: J. Harezlak: None. A. Shah: None. B.D. Stemper: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.10/PP8

Topic: J.07. Data Analysis and Statistics

Support: NIH RF1MH125933

Title: Multiview Integration of Brain Morphometry, Connectivity, and Transcriptomics Reveals Shared Gene-Regional-Network Pathways

Authors: *N. SARDARIPOUR¹, N. HOANG², W. WU², K. SCHILLING⁴, S. MANSOUR L.⁵, A. ZALESKY⁶, J. CAPRA⁷, M. RUBINOV³;

²Computer Sci., ³Biomed. Engin., ¹Vanderbilt Univ., Nashville, TN; ⁴Vanderbilt Univ. Inst. of Imaging Sci. (VUIIS), Nashville, TN; ⁵The Univ. of Melbourne, Melbourne, Australia;

⁶Melbourne Neuropsychiatry Ctr., Melbourne, Australia; ⁷Epidemiology and Biostatistics, Bakar Computat. Hlth. Sci. Inst., San Francisco, CA

Abstract: Objective: Understanding multiscale relationships between brain gene expression, morphology, and network organization remains a major challenge in systems neuroscience. Here, we describe a recursive multiview canonical correlation analysis framework that uncovers these relationships by integrating transcriptomic, morphological, and connectomics data into a unified latent space.

Methods: We developed a non-negative regularized mvCCA with recursive feature pruning to identify stable cross-modal associations between data on gene expression, brain morphology, and network organization from European ancestry subsets of 39,565 UK Biobank subjects (mean age 64.4 ± 7.7 years, 52% female). We imputed gene expression for 8 brain regions using Joint-Tissue Imputation trained on post-mortem data from the GTEx project. We combined this expression with regional brain volume, thickness and area, extracted from T1w MRI using FreeSurfer (Desikan-Killiany atlas). We also adopted network-level features from diffusion MRI tractography using Schaefer and Melbourne subcortical atlases.

Results: We found significant multiview associations linking gene expression, regional morphometry, and network connectivity (Region-Network: $R_{\text{test}}=0.56$, Region-Gene: $R_{\text{test}}=0.15$, Network-Gene: $R_{\text{test}}=0.09$; $p<0.001$), with the strongest regional weights in dorsolateral prefrontal and anterior cingulate cortices. Selected gene-network features highlighted sensory-motor, default mode, attention, and limbic circuits. Key genes (CLU, BID, BRD3, PIK3CD) implicated neurodegeneration, synaptic plasticity, vascular regulation, and immune pathways. GWAS Catalog and PredixVU enrichment analysis revealed significant associations ($p<0.05$) with neurodegenerative (dementia), neuropsychiatric (depression, ADHD, suicidal ideation), immune (lymphocyte count, asthma), and vascular traits. Collectively, our framework describes an integrated approach that goes beyond bi-modality associations to link gene-regional-network patterns with cognitive and pathological phenotypes.

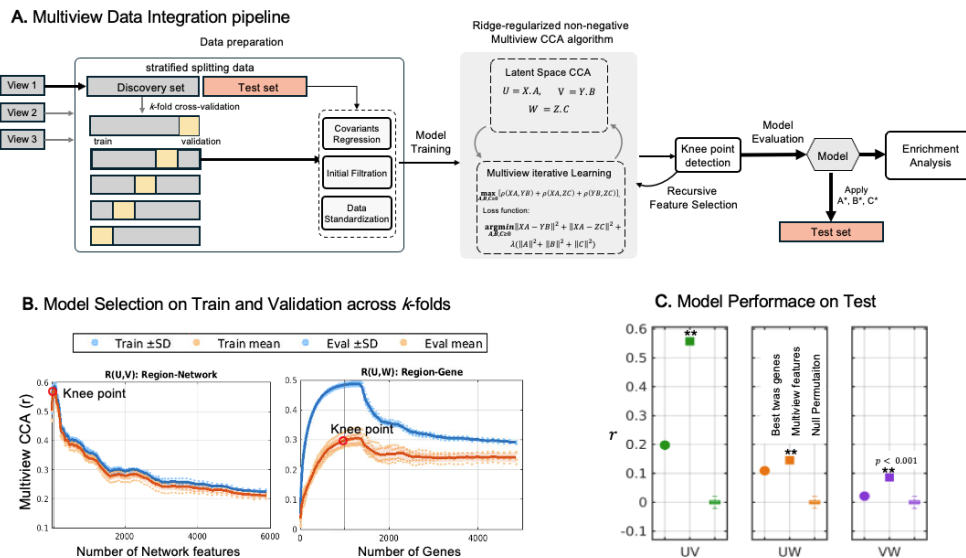


Figure: Recursive multiview canonical correlation analysis (mvCCA) framework for integrative neurogenomics.

(A) Multimodal data (morphometry, gene expression, connectivity) were integrated via ridge-regularized non-negative mvCCA. Recursive feature pruning with knee detection selected stable gene-network features, evaluated on held-out data with enrichment analysis.

(B) Model selection via iterative pruning of low-weight features; knee points define optimal gene and network subsets across folds.

(C) Test set canonical correlations confirm significant multiview associations.

Disclosures: N. Sardaripour: None. N. Hoang: None. W. Wu: None. K. Schilling: None. S. Mansour L.: None. A. Zalesky: None. J. Capra: None. M. Rubinov: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.11/PP9

Topic: J.07. Data Analysis and Statistics

Support: CAPES- BRAZIL – Financing Code 001
FAPESP (2023/17468-7)

Title: Serotonin syndrome in a psychiatric hospital: incidence and proposal of new diagnostic algorithm

Authors: *L. R. POIAN¹, S. CHIAVEGATTO^{2,3};

¹Pharmacol., Univ. of São Paulo, São Paulo, Brazil; ²Pharmacol., Biomed. Sci. Inst. - Univ. of Sao Paulo, Sao Paulo, Brazil; ³Psychiatry, Inst. of Psychiatry, University of Sao Paulo, Brazil

Abstract: Introduction The global increase in the prescription of antidepressants and anxiolytics, particularly selective serotonin reuptake inhibitors (SSRIs), has raised concern about the increased occurrence of Serotonin Syndrome (SS). SS is a potentially life-threatening adverse drug reaction caused by excessive serotonergic activity in the CNS. It presents with behavioral, neuromuscular, and autonomic changes. Although severity may vary, early identification is crucial to prevent complications. Diagnosis is clinical and depends on the clinician awareness, which is often lacking, resulting in underreporting and inaccurate incidence estimates. Given this scenario, it is essential to develop an efficient diagnostic algorithm capable of detecting SS across all levels of severity. This study aims to assess the incidence of SS in a psychiatric hospital and propose a new diagnostic algorithm with improved sensitivity and accuracy. **Methods**

We selected 44 drugs reported to be associated with SS. Medical records of patients who received these drugs during 2019 at the Institute of Psychiatry Clinics Hospital, University of São Paulo, were reviewed. Clinical history, medication use, and SS-compatible symptoms were evaluated using Hunter and Sternbach criteria and the Naranjo scale. The study was approved by the Ethics Committees of ICB and HCFMUSP. **Results**

Out of 901 patients who received one or more of the 44 identified drugs, 466 (51.7%) had prescriptions that could potentially predispose them to SS during hospitalization. Of these, four patients were identified with SS, resulting in an incidence rate of 0.86%. Three cases met the Sternbach criteria and one the Hunter criteria; however, none were diagnosed with SS by the medical team. All cases involved SSRIs and second-generation antipsychotics, suggesting a mechanism involving inhibition of serotonin and norepinephrine transporters and muscarinic receptor involvement. To facilitate diagnosis, we propose a new algorithm that increases clinical decision-making confidence by integrating the most widely accepted diagnostic criteria and

using the Naranjo scale to help establish causality across the full spectrum of suspected cases, from mild to severe.

Conclusion

We propose a novel diagnostic algorithm that integrates established criteria with the Naranjo scale, enabling more confident identification and causality assessment across all severities. Our findings suggest that SS is underdiagnosed, even in specialized centers, underscoring the need for enhanced clinical training. Additionally, genetic polymorphisms that increase synaptic serotonin may represent risk factors worth investigating.

Disclosures: L.R. Poian: None. S. Chiavegatto: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.12/PP10

Topic: J.07. Data Analysis and Statistics

Support: NIH/NIAAA Intramural Research Program (ZIA AA000130)
The views, information, or content, and conclusions presented do not necessarily represent the official position or policy of, nor should any official endorsement be inferred on the part of, the Clinical Center, the NIH, or the Dept of HHS.

Title: Identifying drinking patterns in alcohol use disorder using timeline follow-back data

Authors: Z. KUANG¹, X. LI¹, M. SCHWANDT², D. GOLDMAN², N. DIAZGRANADOS², *L. LEGGIO^{3,2};

¹Biostatistics and Clin. Epidemiology Service, Clin. Ctr., ²Natl. Inst. on Alcohol Abuse and Alcoholism, ³Natl. Inst. on Drug Abuse, NIH, Bethesda, MD

Abstract: The Timeline Follow-back (TLFB) method collects self-reported daily alcohol use over a specified period, providing continuous and individualized data on drinking behavior. FDA outcomes for Alcohol Use Disorder (AUD) clinical trials are based on the TLFB. TLFB data can be used to identify distinct drinking trajectories among AUD individuals. Advancing methods for analyzing TLFB data can improve our understanding of drinking patterns and enhance the prediction of related outcomes, such as response to specific treatments, use of other substances (e.g., nicotine, cannabis), psychiatric comorbidities, treatment-seeking behavior, and liver damage. The current study applied heatmap clustering methods to 90-day TLFB data to identify drinking patterns in both treatment-seeking (TS, n = 837) and non-treatment-seeking (NTS, n = 1258) groups (Total, n = 2095). Because individual subject data collection began on different days of the week, data were aligned to the most common last day within each treatment group (Tuesday for TS and Friday for NTS), resulting in a final period of time of 84 days. The aligned data were standardized by column (drinking day). Euclidean distances were calculated and Ward's clustering algorithm was implemented in a heatmap with day on the x-axis. Mean profile

plots were generated. Clinical and demographic factors were analyzed via Chi-squared and Kruskal-Wallis tests. For both treatment groups, four clusters were created. In the TS group, the cluster sizes and mean number of drinks ($\pm$ SD) were: (1) $n=256$, 4.0 ± 4.4 ; (2) 230 , 9.1 ± 6.4 ; (3) 294 , 16.8 ± 7.3 ; (4) 57 , 31.7 ± 8.1 , and for the NTS group: (1) 842 , 0.5 ± 1.2 ; (2) 286 , 3.4 ± 3.7 ; (3) 88 , 7.5 ± 4.3 ; (4) 42 , 15.8 ± 8.2 . The mean profile plots for all the clusters revealed a cyclical pattern in mean number of drinks over time, with an increase in mean number of drinks on Fridays and Saturdays. As the mean number of drinks increased between clusters in the TS group, there was a corresponding increase in Alcohol Use Disorders Identification Test (AUDIT) scores, anxiety scores, ALT and AST levels. Patients in clusters with larger mean number of drinks were more likely to be male, smoke, and use other substances (e.g., cannabis, stimulants). Similar trends were observed in the NTS group among the clusters with heavier drinkers; moreover, those patients were more likely to be older and diagnosed with psychiatric disorders like depression and PTSD. These results suggest the importance of categorizing patients by drinking trajectory into distinct clusters to help develop more personalized treatment plans. Further research should investigate clustering methods that incorporate the longitudinal feature of the data.

Disclosures: Z. Kuang: None. X. li: None. M. Schwandt: None. D. Goldman: None. N. Diazgranados: None. L. Leggio: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.13/PP11

Topic: J.07. Data Analysis and Statistics

Title: Artificial Intelligence Models for Predicting Opioid Use Disorder: A Systematic Review and Meta-analysis

Authors: *Y. LEE¹, C.-H. LEE², J.-E. DING³, Y. HUANG⁴;

¹Taipei Med. Univ., taipei, Taiwan; ²Dept. of Plastic and Reconstructive Surgery, Chang Gung Mem. Hosp., taoyuan, Taiwan; ³Stevens Inst. of Technol., New Jersey, NJ; ⁴Dept. of Psychiatry,, Taipei Med. Univ. Hosp., Taipei city, Taiwan

Abstract: Background: The global opioid crisis has highlighted the urgent need for early identification of individuals at risk of opioid use disorder (OUD). Recent advances in artificial intelligence (AI) and machine learning (ML) have enabled the development of predictive models using complex, high-dimensional healthcare data. However, the extent to which these models are clinically reliable, generalizable, and ethically sound remains unclear. **Objective:** To systematically review and quantitatively synthesize existing evidence on AI-based models designed to predict the risk of OUD and related outcomes, including prolonged opioid use, medication discontinuation, overdose, and mortality. **Methods:** We conducted a systematic review and meta-analysis of 33 original studies that applied AI models—such as logistic

regression, random forest, gradient boosting, and deep learning—to predict opioid-related outcomes. Key data extracted included model type, sample size, input features, prediction targets, performance metrics (e.g., AUROC), and validation strategy. A random-effects meta-analysis was performed on studies reporting comparable metrics. **Results:** The pooled AUROC across 18 eligible studies was 0.78 (95% CI: 0.74-0.82), indicating moderate-to-high predictive performance. Ensemble models generally outperformed conventional approaches. Models trained on structured data, especially electronic health records and claims, achieved better consistency. However, only 27 percent of studies included external validation, and fairness metrics were reported in less than 10 percent. Considerable heterogeneity ($I^2 = 71$ percent) was observed across modeling strategies and outcome definitions. **Conclusion:** AI models demonstrate strong potential in forecasting OUD-related risks, with particular promise in structured healthcare data. However, variability in outcome definitions, lack of validation, and limited transparency present barriers to clinical translation. Future studies should emphasize standardization, prospective evaluation, and ethical considerations to ensure safe integration into practice.

Disclosures: Y. Lee: None. C. Lee: None. J. Ding: None. Y. Huang: None.

Poster

PSTR051: Data Analysis and Statistics: Human Data

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR051.14/PP12

Topic: J.07. Data Analysis and Statistics

Support: Conahcyt PhD grant CVU 891162

Title: Lean six sigma in neuroscience: enhancing drug development through design of experiments

Authors: *G. SANTILLÁN DÁVILA¹, S. E. OCHOA HUGO²;

¹Quality Approvers México, Guadalajara, Mexico; ²Med. Biotech., CIATEJ, Guadalajara, Mexico

Abstract: Design of Experiments (DOE), a statistical methodology originating from Ronald Fisher's foundational work, has become a key component of Lean Six Sigma strategies for optimizing complex systems. In neuroscience drug development, DOE addresses three persistent challenges: experimental variability, prolonged development timelines, and inefficient formulation strategies. DOE has been applied to optimize neuropharmacological compounds such as acetylcholinesterase inhibitors and monoclonal antibodies targeting beta-amyloid in Alzheimer's disease. By systematically manipulating independent variables—such as compound concentration, excipient type, and formulation conditions—DOE enables the identification of statistically significant interactions that influence solubility, bioavailability, and therapeutic efficacy. This structured approach reduces the number of experimental iterations required to reach optimal formulations, significantly shortening development time. In preclinical

neuroscience research, DOE has improved the design of behavioral and pharmacokinetic studies by minimizing confounding variables and enhancing statistical power. This directly addresses a major limitation in the field: the low reproducibility of experimental results due to inconsistent protocols and uncontrolled variability. DOE provides a framework for standardizing experimental conditions, increasing the reliability and comparability of findings across laboratories. By integrating DOE into the early stages of neuroscience drug development, researchers can systematically reduce uncertainty, accelerate decision-making, and generate more robust, translatable data. This methodological shift supports the development of safer, more effective therapies for complex neurological disorders.

Disclosures: G. Santillán Dávila: None. S.E. Ochoa Hugo: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.01/PP13

Topic: J.08. Methods to Modulate Neural Activity

Title: Feasibility of real time intraparenchymal neuro-endoscope using robot attached optical coherence tomography for stereotactic brain surgery in large animal

Authors: *J. HA¹, W. CHANG³, S. HAN³, C. KONG⁴, J. RIM²;

²Dept. of Neurosurg., ¹Severance Hospital, Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; ³Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; ⁴Dept. of Neurosurg., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Background:Stereotactic brain surgery allows precise targeting based on 3D coordinates and detailed anatomy. Safe trajectory planning requires prediction of critical structures along the path and optimal entry point selection.Trajectory accuracy can be reassessed intraoperatively using CT/MRI or microelectrode recording (MER). However, intraoperative imaging is time-consuming, space-limited, and restricts tool dimensions. MER is prone to noise, less accurate under deep anesthesia, and carries hemorrhage risk due to sharp probes. Optical Coherence Tomography (OCT) provides high-resolution imaging via light interference, offering a rapid, safe alternative for intraoperative guidance.Material and Methods:We developed a fiber-optic OCT probe integrated into a conventional MER guide system and inserted stereotactically into brains of live minipigs. After IV sedation, preoperative MRI was obtained. The head was fixed in O-frame for CT imaging. Surgical trajectory was planned using the Kymero robotic system (Ko Young Technologies, Suwon, Korea), based on preoperative MRI, targeting a path through the frontal cortex, ventricle, thalamus, and subthalamus.A burr hole penetrated and dura was opened. MER probes were inserted for recording. In the same passage, the OCT probe was inserted and withdrawn in four directions—dorsal, ventral, medial, and lateral—at 90° intervals, with automatic motor system that was mounted on the target guidance system. Results:The day after surgery, the minipigs were sacrificed, and their brains were extracted, formalin-fixed, and

sectioned for histological analysis. OCT data were cross-validated against corresponding MER signals, pre- and postoperative MRI findings, and histological results obtained from the same trajectories. The resultant correlation revealed that intracranial OCT can differentiate gray matter from white matter, and was able to detect the point of entrance of catheter into cortex or ventricle. Though the MER which was simultaneously implemented clearly designated the point of contact with the thalamus and subthalamic nucleus, on the contrary to our belief, the OCT results were inconclusive in differentiating these deep brain structures. Conclusion: The OCT can provide high-resolution real-time tomographic information which could be useful for stereotactic brain surgery. Its ability to distinguish deep brain structures remains a subject for further optimization.

Disclosures: J. Ha: None. W. Chang: None. S. Han: None. C. Kong: None. J. Rim: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.02/PP14

Topic: J.08. Methods to Modulate Neural Activity

Title: Magnetic field-programmable actuators for scalable magnetogenetic stimulation toward multiplexed neuromodulation

Authors: *J. PARK¹, M. KWAK², L. JAE HYUN³, J. CHEON¹;

¹IBS Ctr. for Nanomedicine, ²Yonsei Univ., Seoul, Korea, Republic of; ³YONSEI UNIVERSITY, SEOUL, Korea, Republic of

Abstract: Multiplexed stimulation of multiple brain sites remains a critical goal in both basic neuroscience and neurotechnology. Such capabilities are essential for investigating complex neural networks and hold strong potential for clinical translation. While brain-computer interfaces, multi-electrode arrays, and optogenetics are powerful tools, their scalability and deep-brain accessibility are constrained by physical and optical limitations. Here, we present a magnetogenetic multiplexing platform that enables selective actuation of multiple neural targets using magnetic nanoparticles responsive to distinct magnetic field patterns. We engineered these nanoparticles with distinct magnetic signatures by tuning their magnetic anisotropy to control the balance between Brownian and Néel relaxation modes. By tuning the nanoparticles' magnetic anisotropy, we control the balance between Brownian and Néel relaxation dynamics to produce torque-based mechanical stimulation. This selective activation enables differential engagement of Piezo1 ion channels in spatially or genetically defined neuronal populations. Our approach establishes a foundation for scalable, field-specific magnetomechanical stimulation and offers a programmable framework for future applications in multiplexed, non-invasive neuromodulation.

Disclosures: J. Park: None. M. Kwak: None. L. Jae hyun: None. J. Cheon: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.03/PP15

Topic: J.08. Methods to Modulate Neural Activity

Title: Magnetogenetic neural inhibition via the mechanosensitive ion channel FLYC1

Authors: *W. SHIN¹, Y. LEE², S. KOO¹, M. KWAK³, J. CHEON⁴;

¹Yonsei university, Seoul, Korea, Republic of; ²Nano Biomed. Engin., IBSCNM, yonsei university, Seoul, Korea, Republic of; ⁴IBS Ctr. for Nanomedicine, ³Yonsei Univ., Seoul, Korea, Republic of

Abstract: Neuromodulation is essential in neuroscience, enabling the control of neuronal activity through excitation or inhibition. While our previous magnetogenetics (MG) system enhanced neuronal activity wirelessly via the Piezo1 ion channel, expanding MG to include inhibitory capabilities is critical for broader application. Here, we introduce the mechanosensitive chloride channel FLYC1 into the MG platform to achieve precise neuronal silencing through magnetic stimulation. We demonstrate that magnetically induced gating of FLYC1 enables robust inhibition of neuronal activity. Targeted inhibition of the paraventricular nucleus (PVN) in a restraint-induced stress (RIS) mouse model leads to significant improvements in stress-related molecular and behavioral outcomes. This work presents a noninvasive, remote-control, and genetically targetable strategy for neuronal inhibition, complementing existing excitatory MG tools. The integration of FLYC1 broadens the utility of magnetogenetics, offering a versatile platform for bidirectional modulation of neural circuits in diverse neuroscience research and potential therapeutic applications.

Disclosures: W. Shin: None. Y. Lee: None. S. Koo: None. M. Kwak: None. J. Cheon: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.04/PP16

Topic: J.08. Methods to Modulate Neural Activity

Title: Tri-split Piezo1 for AAV-based delivery and mechanobiology application

Authors: *Y. LEE¹, J. PARK², W. SHIN³, S. LEE¹, M. KWAK⁴, J. CHEON⁵;

¹IBSCNM, yonsei university, Seoul, Korea, Republic of; ²IBS Ctr. for Nanomedicine, Yonsei Univ., Seoul, Korea, Republic of; ³Yonsei university, Seoul, Korea, Republic of; ⁵IBS Ctr. for Nanomedicine, ⁴Yonsei Univ., Seoul, Korea, Republic of

Abstract: Piezo1 is a mechanosensitive cation channel that plays a crucial role in various physiological processes by responding to mechanical stimuli and mediating calcium influx.^{1,2} Piezo1 gene delivery holds potential for neuromodulation through mechanical force and the regulation of various calcium-mediated pathways.³⁻⁵ Additionally, its dysfunction has been associated with diverse physiological abnormalities.^{6,7} Despite its importance, the large size of the Piezo1 gene (7.7 kb) poses a major challenge for gene delivery, particularly with Adeno-Associated Virus (AAV)-based vectors, which have a packaging limit of ~4.7 kb. Overcoming this limitation is crucial for enabling efficient Piezo1-based genetic studies and potential therapeutic applications. Here, we show that the Piezo1 protein can be functionally reconstituted by splitting it into three fragments, named Tri-Split Piezo1 Fragments (TPF), and co-expressing them. We identified optimal split sites between transmembrane helical units 4 and 5, and 7 and 8, resulting in TPF1 (2.3kb), TPF2 (2.5kb), and TPF3 (2.8kb), which are compatible with AAV packaging. Our results demonstrate that these fragments successfully reassemble into a functional Piezo1 channel, as confirmed by membrane localization and activation using the Piezo1 agonist Yoda1 and physical stimuli. This finding suggests a viable approach to overcoming size limitations in gene delivery and provides a framework for expanding the use of mechanosensitive channels in vivo applications

Disclosures: Y. Lee: None. J. Park: None. W. Shin: None. S. Lee: None. M. Kwak: None. J. Cheon: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.05/PP17

Topic: J.08. Methods to Modulate Neural Activity

Title: Non genetic in vivo bimodal neuromodulation using gold nanorods-mediated photothermal stimulation

Authors: *C. YOON^{1,2}, S. PARK³;

¹Korea Advanced Inst. of Sci. and Technol., Seoul, Korea, Republic of; ²Seoul Natl. Univ., Seoul, Korea, Republic of; ³Seoul Natl. Univ., Seoul.

Abstract: Brain-computer interfaces (BCIs), once limited to research tools when first introduced by Michigan probe or Utah array, are now redefining human interaction with the digital world. However, current BCIs remain unidirectional—capable of translating brain activity into digital signals but lacking the effective means to deliver signals back into the brain. Because genetic tools such as optogenetics and chemogenetics are difficult to apply in human applications, there remains a need for reliable non-genetic neuromodulation platforms to establish a bidirectional BCI. In this study, we present a non-genetic, in vivo bimodal neuromodulation platform by integrating a fiber-based multifunctional neural probe with gold nanorods (GNRs), laying the foundation for bidirectional BCI. The neural probe was fabricated via thermal drawing. A

polycarbonate (PC) rod wrapped in a PMMA tube formed an optical waveguide, followed by wrapping of additional PC layers. Three grooves were carved using computer-guided cutting and enclosed within a final PC tube to produce a thermoplastic preform to make a thermoplastic rod, or preform, embedding an optical waveguide surrounded by three hollow channels. Two tungsten microwires were inserted into two of these channels and co-drawn with the preform, preserving the internal structure while reducing dimensions. The resulting fiber embedded an optical waveguide, two tungsten electrodes, and a microfluidic channel, which were subsequently interfaced with an optical ferrule, two socket connectors, and tubing respectively. GNRs were synthesized using a conventional seed-mediated method and coated with PEG 3k-cholesterol to enhance biocompatibility and cellular adhesion. The probe was implanted into the mouse hippocampus, and GNR colloid was delivered through the microfluidic channel. Upon near-infrared (NIR) irradiation through the optical waveguide, GNRs generated heat via localized surface plasmon resonance (LSPR), inducing photothermal stimulation that modulated the physical properties such as membrane capacitance and ion conductance in nearby neurons. Electrophysiological recordings showed that moderate, continuous NIR stimulation induced inhibitory neuromodulation. On the other hand, high-intensity NIR pulses delivered to the dentate gyrus significantly increased c-Fos expression relative to the contralateral region, confirmed via immunohistochemistry. This system, integrating fiber-based multifunctional neural probe and GNR-mediated photothermal stimulation, enables non-genetic, spatiotemporally confined neuromodulation and represents a step toward bidirectional BCIs.

Disclosures: C. Yoon: None. S. Park: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.06/PP18

Topic: J.08. Methods to Modulate Neural Activity

Title: Constructing Hierarchical Neuronal Circuits via Nanoimprinted Substrates-Guided Axonal Architecture

Authors: *S. TSENG¹, E. HWANG²;

²Dept. of Biol. Sci. and Technol., ¹Natl. Yang Ming Chiao Tung Univ., Hsinchu City, Taiwan

Abstract: This project introduces a cost-effective, simplified multilayer neuronal culture system using nanoimprinted ethylene-vinyl acetate (EVA) substrates to direct axonal growth and engineer structured neural circuits *in vitro*. Conventional multilayer models, such as organoids and microfluidic systems, pose challenges including high cost, low reproducibility, and limited structural control. By leveraging groove-mediated axonal growth on topographically modified EVA surfaces, this platform offers precise spatial control over axonal alignment and connectivity. Our data demonstrate a developmental transition in axon orientation - from perpendicular to groove direction in the early stage ($\leq$ DIV 4) to parallel alignment in the later

stage ($\geq$ DIV 7). We found that this temporal transition is linked to the actin cytoskeleton, as the administration of actin depolymerizing compound alters the directional guidance. Additionally, we found that surface grooves modulate growth cone morphology and directionality. Interestingly, we discovered that modulating the size of the growth cone also influences the orientation of the axon growth. By controlling the specific axon orientation pattern on the topographically modified EVA surfaces, we can establish a hierarchical neural circuit on a single surface. This approach offers a novel platform for investigating neural network dynamics under spatial constraints. It overcomes the limitations of existing multilayer systems by combining topographical engineering and pharmacological modulation, paving the way for accessible, reproducible, and physiologically relevant neural culture platforms in basic and translational research.

Disclosures: S. Tseng: None. E. Hwang: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.07/PP19

Topic: J.08. Methods to Modulate Neural Activity

Title: Development and applications of an open-source behavioral control system for rat neural recordings

Authors: *H. MILLS;

Univ. of Maryland, Col. Park, Washington, DC

Abstract: At the heart of mammalian cognition lies the ability to plan and make predictions. It facilitates our ability to link sensory information with outcomes and choose appropriate actions - critical abilities for species success. How is sensory information integrated with predictions about impending outcomes, their features, and the actions we take to obtain them? What neural circuits give us the ability to transform sensory input into thoughts about “what comes next, and how to get there”? To address these questions, there is an increasing emphasis on the importance of effectively integrating complex behavioral tasks with neural recordings and manipulations. Despite this, there are a limited number of commercially available behavioral control systems. Those that are available are costly and restricted in scope, especially recording neural activity during behavior. In addition to this they are often limited in the number and type of compatible input/output devices and utilize less flexible programming languages. To aim in bridging these gaps, we designed and implemented rat behavioral box systems with custom features that meet the necessary requirements for recording neural activity during complex behavioral tasks. They are constructed from laser-cut stainless-steel components and 3D printed brackets, making them durable, cost-effective, simple to assemble, and therefore readily implemented in any lab. They are operated by open-source Arduino boards, making their setup, programming, and use straightforward while also permitting up to 70 input/output devices. While ongoing work in the

laboratory is focused on utilizing these behavioral systems to record neural activity during an olfactory discrimination learning task designed to assess rats' ability to make predictions and choose appropriate actions, the modularity and open-source nature of this system will permit easy adaptation to meet constantly evolving experimental needs of the lab and the broader fields of neuroscience and behavior. The present data will include behavioral neurophysiology data acquired using our open-source systems in addition to resources for adopting them that will be freely available to the broader science community.

Disclosures: H. Mills: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.08/PP20

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant MH135814

Title: Lightweight wireless headstage for small and large animal electrophysiology research

Authors: J. C. MORIZIO¹, R. J. GERTH², *C. L. HOWARD², V. GO¹;

¹Duke Univ., Durham, NC; ²Spike Neuro, Ann Arbor, MI

Abstract: Spike Neuro and the Wireless Electrophysiology laboratory at Duke University, Department of Electrical and Computer Engineering are working to address issues limiting wireless data transmission technology for electrophysiology research, particularly in small animal research. Current wireless technology requires large and heavy batteries for the transmission of high-fidelity single-unit signals and do not provide electrical stimulation pulses. The weight of these batteries is often prohibitive for small animal models. Our development of novel lightweight, low-power wireless solutions will allow researchers to conduct more complex awake behaving experiments in a wide variety of animal models, better informing our understanding of the nervous system. As reported in our previous work, our lightweight Bluetooth Low-Energy (BLE) solution, designed for mice, provides 4 channels of single-unit recording weighing < 2.7 g and requires only 6 mA (6 hours runtime with a small 40mAh battery). We have achieved transmission of simulated data over 15 ft while meeting power consumption goals and maintaining a low bit error rate. Our wireless Hybrid Backscatter (HBS) solution, designed for rats and larger animals, leverages Quadrature Phase-Shift Keying (QPSK) to encode the neural signal allowing us to increase channel count (up to 64 channels) without a substantial increase in power consumption over the lighter BLE design (9 mA). We have made several improvements on our previously presented prototype that move us closer to a commercializable device. We have incorporated a compression algorithm into our BLE design to improve data transmission bandwidth without requiring additional power consumption. We have also evaluated the BLE performance with different receiver antenna orientations to provide

future customers with valuable set up information to ensure the best performance. These tests identified an ideal antenna orientation that resulted in a packet loss of less than 0.08% at 15ft. We have also built a software plugin for the open-source Open Ephys software for this system. For the HBS design, we have increased the fidelity of our QPSK demodulation to provide improved wireless data transmission. These two wireless solutions will soon provide researchers with useful tools for exploring the neural basis of natural behaviors across a wide range of animal models over extended time periods. In our future work we will conduct *in vivo* testing with these devices.

Disclosures: **J.C. Morizio:** 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.; James Morizio. **R.J. Gerth:** A. Employment/Salary (full or part-time): Rebecca Gerth. **C.L. Howard:** A. Employment/Salary (full or part-time): Charla Howard. **V. Go:** 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.; Vinson Go.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.09/QQ1

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant R01NS110893
NIH Grant R01DC 018300
Australia NHMRC Ideas Grant APP1187416

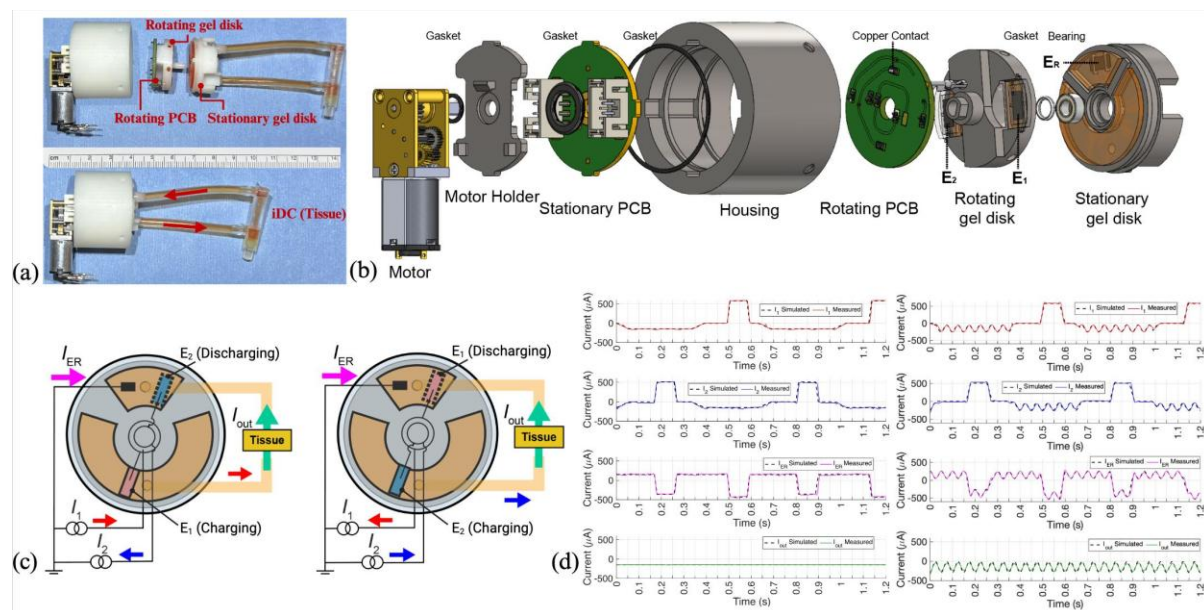
Title: Rotational Freeform Stimulator for Non-Pulsatile Neuromodulation and Pathway to Versatile Neural Implants

Authors: ***K. CHENG**¹, P. LI², R. M. VARGHESE¹, G. E. FOXWORTHY¹, G. Y. FRIDMAN³, W. M. THOMAS³;

¹Biomed. Engin., ²Mechanical Engin., ³Otolaryngology, Johns Hopkins Univ., Baltimore, MD

Abstract: Conventional neural implants deliver charge-balanced biphasic pulses producing phase-locked excitation, limiting graded inhibition and natural stochastic firing patterns. Ionic direct current (iDC) stimulation can directly excite, inhibit, and sensitize neurons, but chronic iDC delivery without electrochemical reactions has been challenging. Our lab developed the Freeform Stimulator (FS), rectifying charge-balanced pulses into iDC using microfluidics. However, shape memory alloy (SMA) prototypes suffered low reliability, limited charge capacity, and short lifetimes due to thermal constraints. To overcome these limitations, we developed a Rotational Freeform Stimulator (RFS) addressing these limitations. The RFS

employs seven components: DC motor, housing, stationary/rotating PCBs, and gel disks with stainless steel electrodes ($5.8 \times 2.8 \text{ mm}$). Controlled disk rotation rectifies biphasic pulses into arbitrary ionic waveforms, with agar gel blocks providing ionic pathways. An eight-state algorithm coordinates two current sources with 1ms sampling to maintain electrode charge balance during continuous iDC delivery. Performance testing ($n=3$) demonstrated stable iDC across $\pm 200 \mu\text{A}$ with $< 5 \mu\text{A}$ ripple ($< 1\%$ variation). The RFS generated DC and sinusoidal waveforms up to 20Hz with high fidelity, confirmed via voltage measurements using instrumentation amplifiers. Load testing showed robust performance across tissue impedances up to $120 \text{ k}\Omega$ with 24-hour operational integrity. The rotational design eliminated thermal constraints, reduced power consumption, and improved reliability versus SMA actuators. Dual-channel experiments validated simultaneous multi-electrode operation without interference. Unlike conventional pulsatile stimulation producing artificial phase-locked responses, the RFS enables natural neural modulation preserving stochastic firing patterns. This expands therapeutic applications for chronic pain, and neurological conditions requiring graded inhibition, providing a path toward chronic implantable iDC systems.



Disclosures: K. Cheng: None. P. Li: None. R.M. Varghese: None. G.E. Foxworthy: None. G.Y. Fridman: None. W.M. Thomas: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.10/QQ2

Topic: J.08. Methods to Modulate Neural Activity

Support: CDMRP HT9425-24-1-0018
Chuck Noll
PITA

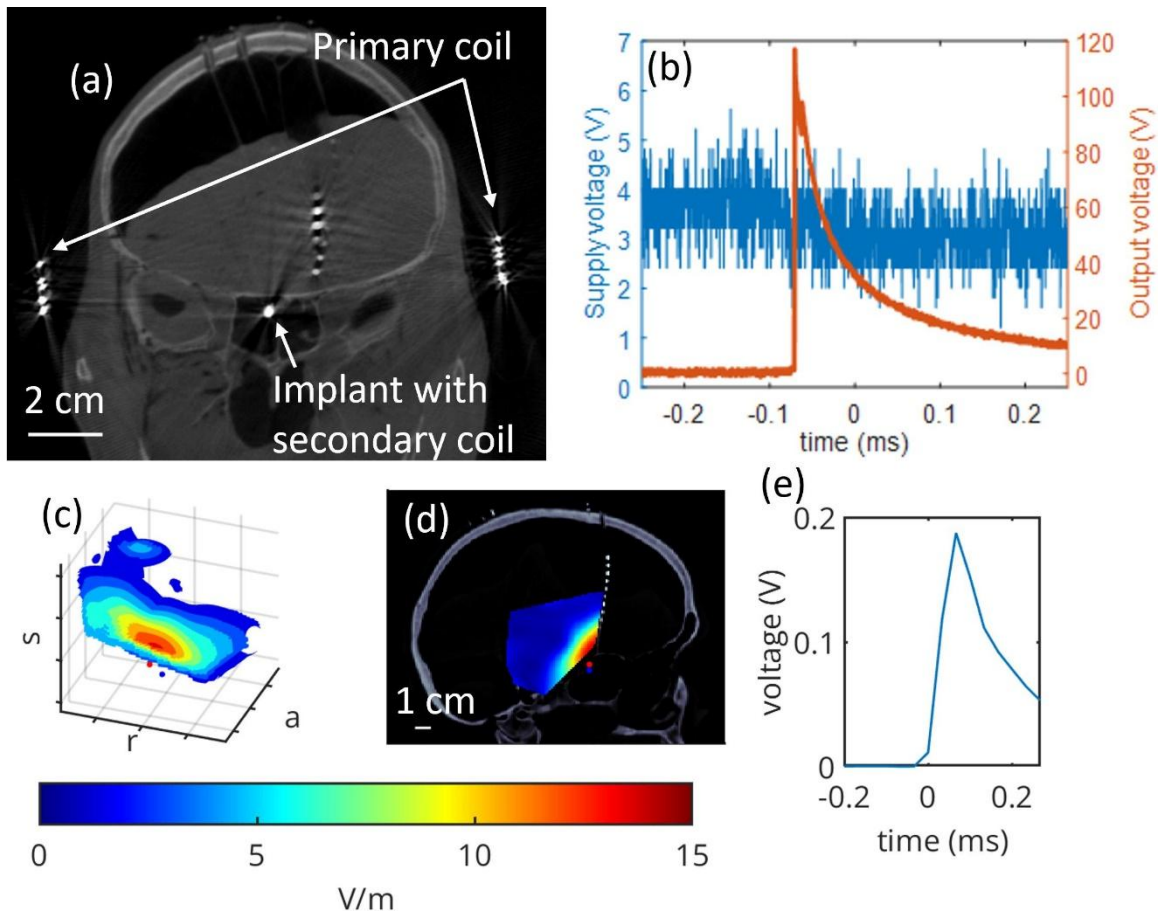
Title: Wireless sphenoid implant for transnasal deep brain stimulation

Authors: *M. FORSSELL¹, D. KUSYK³, R. TUSI¹, B. CHENG⁴, A. WHITING³, E. WANG⁵, P. GROVER²;

²Electrical & Computer Engin., ¹Carnegie Mellon Univ., Pittsburgh, PA; ³Neurosurg.,

⁴Allegheny Hlth. Network, Pittsburgh, PA; ⁵Univ. of Pittsburgh Med. Ctr., Pittsburgh, PA

Abstract: Stimulation of deep brain regions is a valuable clinical technique for treatment of neural disorders such as parkinsonian tremor and obsessive-compulsive disorder, and shows promise for an even broader range of mental health conditions such as depression and addiction. However, the invasive nature of the surgery required to implant the probes and implantable stimulators limits the patient population that can benefit from deep brain stimulation (DBS). We are proposing a novel, minimally-invasive avenue for DBS using electrodes inserted through the nose and placed on the inferior surface of the skull, in the sphenoid sinus and the olfactory cleft. The sphenoid sinus, a 1 to 2 cm-diameter air-filled cavity located under the bottom of the skull, is accessed from the nasal cavity through a narrow opening (1 x 2 mm² on average) known as the sphenoid ostium. We designed a miniature implanted stimulator (3 x 4 x 10 mm³) that can be inserted into the sphenoid sinus through the nose using a minimally invasive endoscopic procedure, including a sphenoidotomy to enlarge the ostium and allow the device to be inserted. The implant consists of a low-power stimulation circuit, operating from a 3 V supply and able to output high-voltage (up to 50 V) exponential pulses across two 3 mm diameter electrodes. We have tested the insertion of the implant in two cadaveric heads, where we measured the electric fields elicited by the stimulator. We obtained large (>10 V/m) focused fields in inferior brain regions. We have also demonstrated wireless powering of the implant using inductive power transfer. An elliptical primary coil (n=7 turns, 22 cm major axis, 16 cm minor axis), was placed around the outside of the head, coplanar with the implant inserted in the sphenoid sinus. The secondary coil, connected to the implant, consists of a flexible PCB spiral with outer diameter 4 mm (width=60 μ m, spacing=60 μ m, n=9 turns). We were able to power the implant to 3 V by applying 2.4 W through the primary coil (12W peak at a 20% duty cycle). Simulations determined that the specific absorption rate (SAR) is 2.8 W/kg, below the 10 W/kg safety limit.



(a) Alignment of primary coil around the head with secondary coil in the sphenoid sinus. (b) Wirelessly powered implant operation, achieving $>3V_{DC}$ supply voltage and >100 V output pulses. (c,d) Measured electric field elicited by the implant. (e) Pulse shape measured in the brain

Disclosures: M. Forssell: None. D. Kusyk: None. R. Tusi: None. B. Cheng: None. A. Whiting: None. E. Wang: None. P. Grover: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.11/QQ3

Topic: J.08. Methods to Modulate Neural Activity

Support: Samsung Advanced Institute of Technology (SAIT), Samsung Electronics

Title: Network intracellular recording and synaptic connection mapping with a microhole electrode array

Authors: *J. WANG;
Virginia Tech., Blacksburg, VA

Abstract: Finding synaptic connections and defining their strengths across neuronal networks is a paramount challenge in neuroscience. Electron microscopy can image connections but cannot determine strengths. Patch clamp recording with intracellular sensitivity can measure synaptic signals to identify and characterize synaptic connections, but only from few neurons. Network-wide parallelization of such intracellular recording could bring synaptic connectivity mapping closer to reality, but has proven difficult, mapping hitherto ~300 connections. Here we report a 4,096 microhole electrode array on a semiconductor chip, which transforms parallel intracellular recording into a broadly accessible routine yet powerful for synaptic connectivity mapping. It is easy to fabricate yet achieves an exceptional 90% (3,685 of 4,096 electrodes) average intracellular coupling rate with high coupling fidelity, generating network-wide intracellular recording data from rat neuron cultures that carry synaptic signals in unprecedented quantity. From these, we extract 70,000+ plausible synaptic connections amongst 2,000+ neurons, and catalog them into inhibitory, weak/uneventful excitatory, and strong/eventful excitatory chemical synaptic connections (0.7%, 89.4%, and 5.7%) as well as electrical synaptic connections (4.2%), with an estimated overall error rate of around 5%. This scale of mapping unprecedented in electrode technology, with the ability to qualify--potentially quantify--connections, may help a step toward functional synaptic cartography.

Disclosures: J. Wang: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.12/QQ4

Topic: J.08. Methods to Modulate Neural Activity

Support: No.2022ZD0210300

Title: An ultraflexible, high-density microelectrode array for precise and clinically effective deep brain stimulation

Authors: *Z. WANG¹, Q. DONG², Z. YAN², F. ZAN³, X. LI², C. REN¹, Z. ZHAO¹;
¹Inst. of Neurosci. (ION), Chinese Acad. of Sci., Shanghai, China; ²Air Force Med. Univ. of PLA (the Fourth Military Med. University), Xi'an, China; ³The Hong Kong Univ. of Sci. and Technol. (Guangzhou), Guangzhou, China

Abstract: Deep brain stimulation (DBS) is one of the most important clinical advances for treating neurological and psychiatric disorders. However, conventional rigid electrodes often

require relatively high stimulation currents, causing diffuse electric fields that lead to off-target effects and reduced clinical precision. Here, we present an **ultra- Flexible, Implantable Neural Electrode array (uFINE-stim)** developed for spatially precise and stable neuromodulation at low current levels. In vitro characterization demonstrated enhanced electrochemical performance, including increased charge injection capacity and improved stimulation durability. In vivo two-photon calcium imaging in the mouse cortex revealed that uFINE-stim significantly reduced current thresholds for neural activation and improved spatial specificity compared to rigid electrodes. Moreover, when applied to DBS of the subthalamic nucleus (STN) in a Parkinson's disease (PD) mouse model, uFINE-stim enabled substantially lower therapeutic current thresholds and improved long-term stability of neuromodulation. Finite-element modeling further indicated that uFINE-stim could generate more focal electric fields, facilitating highly targeted and personalized neuromodulation. Critically, intraoperative studies in awake PD patients demonstrated that simultaneous multichannel stimulation using uFINE-stim effectively alleviated clinical symptoms, achieving outcomes comparable to standard clinical DBS electrodes but at substantially lower total charge levels. Together, these findings underscore the translational potential of ultraflexible, multichannel microelectrode arrays to enable safer, more precise, and personalized neuromodulation therapies.

Disclosures: **Z. Wang:** None. **Q. Dong:** None. **Z. Yan:** None. **F. zan:** None. **X. Li:** None. **C. Ren:** None. **Z. Zhao:** None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.13/QQ5

Topic: J.08. Methods to Modulate Neural Activity

Title: Inkjet-printable strain-compliant bioelectronics for accessible dynamic neural interfaces

Authors: ***J. LEE;**

Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Electrical stimulation of the central nervous system (CNS), first demonstrated in the 19th century, laid the foundation for neural interfaces—devices that monitor and modulate neural activity. Among the earliest clinical applications, spinal cord stimulators (SCS) were developed to treat chronic pain via electrical pulses delivered to the spinal cord. Despite ongoing advancements, conventional SCS devices remain mechanically rigid, posing risks of tissue damage in the soft, dynamic spinal cord, which undergoes up to 15% strain during normal motion. Additionally, reliance on complex MEMS fabrication limits customization, rapid prototyping, and cost-effective production. To address these issues, researchers have developed soft, stretchable interfaces using materials like thin metal films, conductive polymers, and silicones, which better match tissue mechanics and reduce chronic injury. However, most still depend on MEMS-based methods. In contrast, 3D printing offers a low-cost, customizable

alternative, enabling rapid iteration without cleanroom infrastructure. To leverage the advantages of 3D printing, we developed an inkjet-printed neural interface composed of stretchable silicone and conductive silver-particle composites. The fabrication process is straightforward and requires only minimal post-processing steps, eliminating the need for complex intermediate procedures. With a printing resolution of approximately 100 micrometers, our approach can produce delicate interfaces suitable for the spinal cord's intricate structures. Furthermore, each device can be fabricated in under 15 minutes, enabling rapid customization of interface designs from the same base materials for both spinal cord and muscle surface applications. By using a silicone substrate, our interface attains a mechanical modulus similar to that of the spinal cord dura mater and can sustain strains well beyond physiological ranges without losing conductivity, while substantially increasing biocompatibility. We demonstrate that our interface can remain implanted within the subdural space for two weeks, deliver effective spinal cord stimulation to elicit muscular responses, and induce significantly less structural and phenotypical tissue damage over the long term.

Disclosures: J. Lee: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.14/QQ6

Topic: J.08. Methods to Modulate Neural Activity

Support: DFG 401023906

Title: Miniaturized polyimide based thin-film twisted pair structures for applications in active neural implants

Authors: *J. MARTENS, R. KISS, T. STIEGLITZ;

Lab. for Biomed. Microtechnology, IMTEK-Dept Microsystems Eng, Univ. of Freiburg, Freiburg, Germany

Abstract: Relevance of active thin-film neural implants remains unchanged with constant and evolving advancements in medical engineering. Thin-film technology allows for biocompatible, flexible, and reliable implants while keeping cross-sections to a minimum. As in all electronic devices, active medical implants can suffer from external electromagnetic interference inducing noise into conducting tracks. Such tracks either connect multiple stimulation sites or implantable electronic circuits (μ ASICs) to each other, where noise will lead to wrong signal readings and hence wrong recording or stimulation of neural signals. In larger scale systems, twisted pairs (TP) are commonly used to address these problems and improve digital communication resilience. Not only do they improve noise immunity from aggressor lines, but they also minimize electromagnetic interference from themselves to neighboring parts of the same system allowing higher data transfer rates. In an increasingly wirelessly interconnected world,

interference by electromagnetic waves should not be underestimated and must be considered as early as in the design phase of a device. Packaging of electronic components within a hermetic metal enclosure (e.g. as for cardiac pacemakers) is not always feasible. Therefore, this work presents a possibility to realize such miniaturized TP structures based on polyimide (PI) thin-film technology, with the aim of mitigation of electromagnetic interference in neural implants. TP were realized with common micro-electromechanical systems (MEMS) processes in an ISO class 4 cleanroom. The process consisted of a 3-layer stack with two sandwiched platinum metal layers in between. In the course of a dimension analysis, this allowed for feature sizes as small as 10 μm (biggest = 30 μm) with a total layer stack height of 12 μm . Intertwining metal tracks were connected by means of micro-vias with diameters as small as 13 μm (biggest = 40 μm). Depending on the feature size up to 756 vias were employed in a single TP with a universal sample length of 20 mm. Process yield was found to be 100 %, determined by optical characterization (light microscopy, scanning electron microscopy (SEM)) and electrical DC resistance measurement. Bending tests with subsequent resistance measurements were performed to investigate mechanical stability. No failure of any sample could be observed after 10^5 bending cycles. In conclusion, the fabrication of miniaturized TP for application in PI-based neural implants is possible. Future experiments will provide insight on the frequency dependent behavior of the TP, as well as their ability to mitigate incoming and outgoing electromagnetic waves.

Disclosures: J. Martens: None. R. Kiss: None. T. Stieglitz: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.15/QQ7

Topic: J.08. Methods to Modulate Neural Activity

Title: An open source system for microneurography recordings and intraneural microstimulation in humans

Authors: *R. H. WATKINS¹, G. BRAYSHAW², J. P. DUNHAM², B. WARD-CHERRIER², R. ACKERLEY³;

¹CNRS- Aix Marseille Univ., Marseille, France; ²Univ. of Bristol, Bristol, United Kingdom;

³Ctr. de Recherche en Psychologie et Neurosciences, CNRS - Aix-Marseille Univ., Marseille, France

Abstract: Microneurography experiments in human participants have provided us with invaluable insights into human peripheral nerves for over 50 years. Studies on peripheral encoding of touch and its relation to perception have been conducted mainly on the hands, such as linking tactile detection to A β low-threshold mechanoreceptor afferent firing (Vallbo & Johansson, 1979, J Physiol), but also on other sites, such as the forearm, relating C-fiber low-threshold mechanoreceptor activity modulated by the speed and temperature of stroking to

pleasantness (Ackerley et al., 2014, J Neurosci). Further, it is possible to combine this recording technique with intraneural stimulation and evoke specific touch percepts linked to the activation of individual afferents (Vallbo et al., 1984, Brain). A limitation of these approaches is the lack of equipment that meets the experimental requirements and has certification for use in humans. There is a commercial recording system available, but this offers little flexibility for complex experiments, such as needed for precise timing of combined equipment and for microstimulation. We have previously developed a more flexible system for use in neuroimaging setups (Glover et al., 2017, J Neurosci Meth), but this nevertheless required proprietary commercial equipment and was not suitable for recording auxiliary signals such as vibration or force sensors. To meet this need, we have developed a recording and stimulation system for use in microneurography experiments that utilizes open source tools (OpenEphys <https://open-ephys.org/>). This new system incorporates signal isolation in the headstage, which offers a safer approach, and can be used with OpenEphys recording GUI. This alleviates difficulties with previous systems, which require the system to be internally powered and any auxiliary signals to be appropriately isolated (Dunham et al., 2018, Clin Neurophysiol; Glover et al., 2017, J Neurosci Meth). The new system allows the acquisition board to be used with a wide variety of external equipment without the need to purchase separate equipment for acquiring signals from these. This system meets medical isolation requirements and can be adapted for use in both EEG and EMG experiments. This new system also incorporates a simple-to-use constant current stimulator and cross-platform tools for control, which should allow consistent use across different laboratories for studies of the relationship between activation of individual tactile afferents and perception.

Disclosures: R.H. Watkins: None. G. Brayshaw: None. J.P. Dunham: None. B. Ward-Cherrier: None. R. Ackerley: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.16/QQ8

Topic: J.04. Physiological Methods

Title: A microphysiological system on ultra-high-density CMOS-MEA for in vitro functional evaluation with compartmentalized co-culturing neural models

Authors: *X. HAN, N. MATSUDA, M. YAMANAKA, B. NODA, I. SUZUKI;
Dept. of Electronics, Tohoku Inst. of Technol., Sendai, Japan

Abstract: Microphysiological system (MPS) is an in vitro culture technology that reproduces the physiological microenvironment and functionality of humans, and is expected to be applied for evaluating drug efficiency/toxicity. In this study, a MPS device was constructed on a CMOS-MEA platform for compartmentalized co-culture of different types of neurons. And we successfully detected electrophysiological activities in both side of neurons and the synaptic network in micro-channel, which enable evaluation of drug-induced neural responses. The MPS

device was combined to the surface of CMOS-MEA using a directly photobonding method to avoid cell damage. As to mimic a neuromuscular junction (NMJ) model, human iPSC-derived motor neurons and human primary skeletal muscles were cultured in different chambers linked by micro-channels. After culturing for over 4 weeks, spontaneous activity could be detected from both cells. Notably, after electrical stimulation in motor neurons, a corresponding evoked response could be measured in the neighbor skeletal muscle, which indicated the formation of NMJ. By using motor neurons derived from ALS patients, an increasing in spontaneous activity (hyperexcitation) was measured compared to healthy motor neurons. And such hyperexcitation was reduced after Rapamycin treatment. Next, human iPSC-derived sensory neurons and human iPSC-derived spinal cord dorsal horn (SCDH) were cultured on the platform to mimic pain circuit. After adding a TRPA1 agonist AITC to sensory neurons, an acute increasing in spontaneous activity could be measured followed by a slowly increasing in SCDH later, which indicated the signal transduction between different neurons through synaptic networks. The ultra-high-density CMOS-MEA platform provides a single cell level measurement, which enable to detect signal propagation through synaptic network between human iPSC-derived cortical neurons cultured in the MPS device. After administration of linopirdine in one side neurons, specific response could be detected at another side with a time-delay. Taken together, the present compartmentalized MPS device enables co-culture of different peripheral neurons with synaptic network linkage, which is essential to reproduce the relevant human anatomical architecture and for drug assessments by CMOS-MEA.

Disclosures: **X. Han:** None. **N. Matsuda:** None. **M. Yamanaka:** None. **B. Noda:** None. **I. Suzuki:** None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.17/QQ9

Topic: J.04. Physiological Methods

Support: Rosetrees Trust (#CF-2023-I-2_113) Israel Ministry of Innovation, Science, and Technology(#7393)
Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Title: Extracellular recordings from the interior of intact brain organoids enable automated high-throughput functional assay

Authors: ***F. WU**¹, **C. STEADMAN**¹, **B. JAMIESON**¹, **B. CAKIR**², **R. MATHEW**², **E. STARK**³;

¹Diagnos. Biochips, Inc., Glen Burnie, MD; ²Data, A.I., & Genome Sci., Merck & Co., Inc., Lynnfield, MA; ³Neurobio., Univ. of Haifa, Haifa, Israel

Abstract: Translatability between preclinical drug screening models and clinical outcomes remains a significant challenge, with current models often failing to predict human responses accurately. Traditional in vivo studies, while informative, are limited by low scalability, labor-intensive workflows, and their inability to reliably capture human-specific neural dynamics. Brain organoids, derived from human induced pluripotent stem cells (iPSCs), offer a transformative solution by mimicking complex neural circuits and providing a scalable, physiologically relevant in vitro platform for drug discovery. We have developed a fully automated instrument that uses a microfabricated 64-electrode recording probe to capture neural activity from within intact organoids at single-cell spatiotemporal resolution. The robotic system precisely positions the probe inside organoids ranging from 0.3 mm to 3 mm in diameter with real-time feedback, achieving a >95% success rate (n = 129). The workflow, from organoid loading to recording spontaneous spikes, is robust, efficient, and requires minimal expertise, completing within minutes. From the recordings, we extracted and sorted spikes into clusters corresponding to putative single units and classified them as excitatory or inhibitory based on spike waveform characteristics and timing patterns. Spatial mapping of these units across the probe array, spanning up to 300 microns in depth, demonstrated the importance of capturing activity across organoid layers. Monosynaptic connectivity was quantified using Spike Transmission Gain, revealing network interactions within the organoid. Additionally, we used recordings from dorsal and ventral forebrain organoids to train a machine learning model that successfully classified organoid types based on their electrophysiological features. Despite the intrinsic variability of organoids and the stochastic nature of spontaneous spiking, our framework revealed distinct differences between organoid classes, establishing a foundation for using organoid readouts as predictive models. Our ultimate goal is to advance this electrophysiological assay as a scalable, high-resolution readout for organoid-based models, enabling rapid and reliable drug discovery pipelines. This innovation bridges the gap between fundamental research and therapeutic development, offering a powerful tool to address complex neurological and systemic conditions.

Disclosures: **F. Wu:** A. Employment/Salary (full or part-time): Diagnostic Biochips Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Diagnostic Biochips Inc. **C. Steadman:** A. Employment/Salary (full or part-time): Diagnostic Biochips, Inc. **B. Jamieson:** A. Employment/Salary (full or part-time): Diagnostic Biochips, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Diagnostic Biochips, Inc. **B. cakil:** A. Employment/Salary (full or part-time): Merck & Co., Inc. **R. Mathew:** A. Employment/Salary (full or part-time): Merck & Co., Inc.. **E. Stark:** None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.18/QQ10

Topic: J.04. Physiological Methods

Support: NIH Grant 3RF1AG079269
NIH Grant RF1AG079269

Title: Patcherbot agent: artificial intelligence mixture-of-models robot for automated patch clamp electrophysiology

Authors: ***B. MAGONDU**^{1,4}, V. SAXENA², K. STILLWAGON², N. MALTA², C. R. FOREST³;

¹Biomed. Engin., ²Computer Sci., ³Mechanical Engin., Georgia Inst. of Technol., Atlanta, GA;

⁴Biomed. Engin., Emory Univ., Atlanta, GA

Abstract: Patch clamp electrophysiology is the gold standard for single-cell analysis, providing high spatiotemporal resolution for studying electrically active cells and investigating disease mechanisms in neurological disorders. However, it is time-consuming, difficult to master, and low-throughput. Novices often take 6-12 months to become proficient with only a 40-60 % whole-cell yield in a 4-8-hour experiment. Experts with several years of training can push this yield to 70-80 %. User error and fatigue further decrease throughput, especially in brain tissue slices where membrane access is highly variable and where data can be of greater physiological relevance. Previous automation efforts have improved patching efficiency in cultures but still have decreased efficacy in tissue data collection, despite targeting individual steps such as pipette-to-cell localization, cell pipette contact (cell hunting), Gigaohm-seal formation, and membrane break-in. Moreover, these systems still require usage of microscopes, stages, and manipulators to perform initial calibration, a task that may be beyond true beginners. To overcome the aforementioned limitations, we present PatcherBot Agent, an AI-enabled robot that mimics expert behavior and runs unattended. It performs end-to-end pipette and stage calibration, neuron detection, tracking, and recordings without human intervention. These advances increase throughput consistently to those of experts, having achieved over 90% yield in cultured cells, and 70% in slice tissue. By combining object detection, segmentation/tracking, and imitation learning policies for cell hunting, seal formation, break-in, and calibration, this mixture-of-models approach provides the consistency of algorithms alongside the adaptability of human experts, enabling users of any experience level to autonomously obtain electrophysiologically relevant recordings rapidly. This work lowers the barrier of entry for patch clamp electrophysiology by removing the demand for extensive training. By boosting yield and ensuring stable performance, PatcherBot Agent democratizes single-cell electrophysiology and accelerates research in diverse biological systems, bridging the gap between it and other single-cell analytical techniques.

Disclosures: **B. Magondu:** None. **V. Saxena:** None. **K. Stillwagon:** None. **N. Malta:** None. **C.R. Forest:** None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.19/QQ11

Topic: J.04. Physiological Methods

Support: National Natural Science Foundation of China (31930061, 21790394, 31761133016, 31821091, 31330024, 31171026, 31327901, 32171233, 31670843, 21790390, 30125016, 81300139, and 81670313)
National Key Research and Development Program of China (2016YFA0500401)
National Basic Research Program (“973” Program) funded by the Ministry of Science and Technology China (2006CB503800 and 2012CB518006)
Shanxi “1331 Project” Key Subjects Construction

Title: Physiological super-resolution in situ recording reveals kinetics changes of norepinephrine release from sympathetic nerves in a mammalian failing heart

Authors: *B. LIU^{1,2};

¹Chongqing Inst. for Brain and Intelligence, Chong Qing, China; ²Col. of Future Technol., Peking Univ., Bei Jing, China

Abstract: Norepinephrine (NE) in peripheral nervous system (PNS) plays crucial roles in regulating peripheral organs in health and disease. However, the spatiotemporal dynamics of sympathetic-NE release and its underlying mechanisms remain poorly characterized due to technical challenges. Here, we developed and validated a Slice ElectroChemistry (SEC) method to record sympathetic-NE release in heart slices with combined super-resolution and high sensitivity at $1\mu\text{m}\times 1\text{ms}\times 1\text{nM}$ as in patch-clamp recordings. By using SEC method, we revealed the increased NE release, impaired NE reuptake, increased releasable NE-vesicle pool, and impaired vesicle recycling of sympathetic nerves in the heart of transverse aortic constriction (TAC)-induced heart-failure (HF) mouse model, and defined the increased expression of Cav2.2 calcium channel as a central mechanism mediating the facilitation of NE release and thus the pathogenesis of HF, clarifying a longstanding puzzle about the kinetic changes of cardiac sympathetic NE release in HF. Beyond the heart, SEC enables NE release recording in other peripheral organs and human tissues, providing a robust toolset to investigate sympathetic-NE dynamics across diverse pathophysiological conditions.

Disclosures: B. Liu: None.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.20/QQ12

Topic: J.04. Physiological Methods

Title: Automated patch-clamp measurements of action potentials for functional classification and evaluation of hiPSC-derived neurological disease models

Authors: *P. VAELLI¹, S. KARATSIOMPANI², S. SCHACHTELE³, K. R. ROSHOLM⁴;
¹Sophion Biosci., Bedford, MA; ²Novo Nordisk, Malov, Denmark; ³Product Mgmt., FUJIFILM Cell. Dynamics, Madison, WI; ⁴Res. and Develop., Sophion Biosci. A/S, Ballerup, Denmark

Abstract: Human-induced pluripotent stem cells (hiPSCs) are used for the generation of neuronal subtypes and neurological disease models. Electrophysiological measurements of ion channel currents and action potentials are important functional indicators in these models. However, in practice the intercellular variability in functional maturity within a population of hiPSC-derived neurons have made such studies challenging, especially in combination with the low-throughput nature of manual electrophysiological experiments. Here, we demonstrate how automated patch-clamp (APC) measurements of voltage-gated and ligand-gated ion channels in combination with current-clamp measurements of action potentials can be used to identify functionally comparable hiPSC-derived neurons for the evaluation of disease phenotypes. In this study, iPSC-derived glutamatergic neurons were differentiated from a healthy donor using either directed differentiation (iCell GlutaNeurons) or neurogenin-2 overexpression (iCell Induced Excitatory Neurons). An isogenic model of frontotemporal dementia was generated by engineering iPSCs to contain a heterozygous mutation in the progranulin (GRN) gene, resulting in a R493X nonsense mutation replicating the genotype associated with a relatively severe form of the disease. iPSC-derived neuron differentiation is highly reproducible as demonstrated by the robust and consistent expression of the excitatory neuron markers (i.e. β III-tubulin, VGlut1/2, AMPA receptor subunits). To characterize the cells, we first developed an APC assay yielding a whole-cell success rate of ~60%, which allowed measurement of ionic currents from both voltage- and ligand-gated channels, as well as action potentials. We then performed a functional classification based on single-cell action potential firing patterns and demonstrate that this functional classification can be used for evaluating in vitro maturation of iPSC-derived neurons as well as uncovering disease phenotypes in a frontotemporal dementia (GRN) disease model. Our results show: 1) that functional maturity is hampered in GRN neurons, as compared to isogenic control neurons (WT) and 2) a decreased voltage-gated Na⁺ channel density in GRN compared to WT neurons that correlated with action-potential parameters. Together, these data demonstrate that combining APC technology with hiPSC-derived neurons is an accessible high throughput model for evaluating healthy and disease phenotypes, that may benefit drug discovery and target validation using human-relevant models.

Disclosures: P. Vaelli: A. Employment/Salary (full or part-time): Sophion Bioscience. S. Karatsiompani: A. Employment/Salary (full or part-time): Novo Nordisk, Sophion Bioscience. S. Schachtele: A. Employment/Salary (full or part-time): FUJIFILM Cellular Dynamics INC. K.R. Rosholm: A. Employment/Salary (full or part-time): Sophion Bioscience.

Poster

PSTR052: Advances in High Density Electrophysiology Recordings

Location: SDCC Halls B-H

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR052.21/QQ13

Topic: J.04. Physiological Methods

Title: High-throughput automated patch clamp of lysosomal ion channels using Sophion Bioscience platforms

Authors: *G. MOODY¹, E. WALOSCHKOVÁ², A. BARA²;

¹Sophion Biosci., Bedford, MA; ²Sophion Biosci., Ballerup, Denmark

Abstract: In recent years, the interest in lysosomal ion channels for neurodegenerative research has increased substantially. Enhancing clearance of aggregates through lysosomal activation has proposed implications in neurodegenerative diseases such as Parkinson's disease, Amyotrophic lateral sclerosis, and Alzheimer's disease. Traditional whole-cell patch clamp of lysosomes is laborious and extremely specialized. Sophion Bioscience has therefore developed a method for high-throughput automated patch clamp (APC) of enlarged lysosomes (LYSO-Preps provided by Oria Bioscience) using the Qube384TM and QPatch48TM platforms. This APC method involves using small-hole, high-resistant consumables (Qchip Custom and Qplate HiR) for the purpose of capturing organelles and forming tight seals which enable stable recordings of endogenous or modified lysosomal ion channels. We have demonstrated the ability to capture lysosomes with a success rate of 50-70% on the Qube384TM and 70-80% on the QPatch48TM. Further, we are able to record ion channel currents such as TMEM175; and are continuously working together with Oria Bioscience, expanding the panel of lysosomal ion channels available.

Disclosures: G. Moody: A. Employment/Salary (full or part-time): Sophion Bioscience. E. Waloschková: A. Employment/Salary (full or part-time): Sophion Bioscience. A. Bara: A. Employment/Salary (full or part-time): Sophion Bioscience.